STATISTICAL ANALYSIS PLAN
– Region 1–

Study Title:	Phase 2 Study of the Safety, Efficacy, and Pharmacokinetics of G1T28 in Patients with Metastatic Triple Negative Breast Cancer Receiving Gemcitabine and Carboplatin Chemotherapy
Sponsor	G1 Therapeutics 79 T.W. Alexander Drive 4501 Research Commons, Suite 100 Research Triangle Park, NC 27709
Name of Test Drug:	G1T28
Protocol Number:	G1T28-04
Phase:	Phase 2
Analysis Plan Version	Version 1.0
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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aRR	Adjusted Rate Ratio
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under Curve
β-HCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
BOR	Best Overall Response
BPM	Beats Per Minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CDK	Cyclin Dependent Kinase
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	End of Infusion
ESA	Erythropoietin Stimulating Agent
CCI	CCI
CCI CCI	[redacted]
G1T28	Trilaciclib
GC	Gemcitabine and Carboplatin
GCSF	Granulocyte Colony-Stimulating Factor
HR	Hazard Ratio
ICH	International Conference on Harmonization
ITT	Intent-to-treat

Abbreviation	Term
IV	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal Range
MAHE	Major Adverse Hematologic Event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
Nadir	The Lowest Point
NE	Not Evaluable
CCI	[redacted]
NTL	Non-Target Lesion
OC	Observed Case
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
CCI	[redacted]
PP	Per Protocol
PR	Partial Response
CCI	[redacted]
PT	Preferred Term
CCI	[redacted]
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
CCI	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SOC	System Organ Class
SVN	Severe Neutropenia
TEAE	Treatment Emergent AE
TL	Target Lesion
TLFs	Tables, Listings, and Figures
TNBC	Triple Negative Breast Cancer
TPR	Time Point Response
ULN	Upper Limit of Normal Range
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the analyses to be performed following the completion of Study G1T28-04, Phase 2 Study of the Safety, Efficacy, and Pharmacokinetics of G1T28 in Patients with Metastatic Triple Negative Breast Cancer Receiving Gemcitabine and Carboplatin Chemotherapy. The SAP is based on the G1T28-04 Protocol Version 4, dated 31 August 2017.

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database. Any deviations from these guidelines will be documented in the clinical study report (CSR).

The myelosuppression efficacy endpoints and statistical analysis methods described in this SAP are reflective of scientific advice obtained in both the US and EU for evaluation of trilaciclib for the reduction of chemotherapy-induced myelosuppression. While the primary objective of G1T28-04 does not explicitly state that the trial has been designed to evaluate the effects of trilaciclib on chemotherapy-induced myelosuppression, the endpoints of AEs and laboratory values used to evaluate safety and tolerability are the same endpoints used to evaluate effects on chemotherapy-induced myelosuppression. The data collection for this trial was appropriate for the analysis of these myelosuppression endpoints, and the defined endpoints in this SAP are consistent with the overall strategy/rationale for Study G1T28-04.

2. STUDY DETAILS

2.1. Study Objectives

The primary, secondary, and exploratory objectives of this study as defined in the study protocol are presented in Table 1.

Table 1 G1T28-04: Study Objectives

Primary Objective[a]
Assess the safety and tolerability of trilaciclib administered with GC therapy
Secondary Objectives[a]
Assess tumor response and duration of response based on RECIST, Version 1.1
Assess PFS and OS
Assess dose intensity of gemcitabine and carboplatin
Assess the PK profile of trilaciclib
Assess the PK profile of gemcitabine and carboplatin when administered with and without trilaciclib
Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of trilaciclib administered with GC therapy
Assess the incidence of febrile neutropenia
Assess the incidence of infections
Assess the utilization of RBC and platelet transfusions
Assess the utilization of hematopoietic growth factors
Assess the utilization of systemic antibiotics
Assess the incidence of chemotherapy dose reductions and dose interruptions overall
Assess the incidence of Grade 2 or greater nephrotoxicity
Determine the dose schedule of trilaciclib administered with GC therapy
CCI

GC therapy = gemcitabine + carboplatin on Days 1 and 8 or Days 2 and 9 of 21-day cycles; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; CCI ; RBC = red blood cell; CCI ; RECIST = Response Evaluation Criteria in Solid Tumors

CCI

2.2. Study Design

This is a multicenter, randomized, open-label, Phase 2 study of the safety, efficacy, and pharmacokinetics (PK) of trilaciclib in combination with gemcitabine and carboplatin (GC) therapy for patients with metastatic triple negative breast cancer (TNBC). A total of approximately 90 patients will be randomly assigned (1:1:1 fashion) to 1 of the following 3 groups:

- Group 1: GC therapy (Days 1 and 8 of 21-day cycles) only (n=30)
- Group 2: GC therapy (Days 1 and 8) plus trilaciclib administered intravenous (IV) on Days 1 and 8 of 21-day cycles (n=30)

- Group 3: GC therapy (Days 2 and 9) plus trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles (n=30)

The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes at the Post-Treatment Visit.

An independent data monitoring committee (DMC) will perform interim reviews of accumulating safety and disposition data approximately every 4 months during the Treatment Phase of the study, depending upon the enrollment rate. The first DMC meeting will occur after approximately the first 20 patients have been enrolled and completed at least 1 cycle. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.

Criteria for Subsequent Cycles and Study Duration

In all 3 groups, study drug administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator.

Criteria for Day 1/2 of Each Cycle

Patients must meet all of the following criteria to receive the Day 1/2 dose:

- Absolute Neutrophil Count (ANC) ≥ 1.0 × 109/L
- Platelet count ≥ 100 × 109/L
- Nonhematologic toxicities (except alopecia) must be ≤ Grade 2 or have returned to baseline

If the initiation of the next cycle is delayed due to toxicity, the patient should have (at least) weekly visits to follow the toxicity.

Criteria for Day 8/9 of Each Cycle

To receive Day 8/9 dose of each cycle, patients must meet all the following criteria:

- ANC ≥ 1.0 × 109/L
- Platelet count ≥ 75 × 109/L
- Nonhematologic toxicities (except alopecia) must be ≤ Grade 2 or have returned to baseline

If these criteria are not met, the Day 8/9 GC doses should be skipped; no dose reductions or delays are allowed for the Day 8/9 GC doses. If the Day 8/9 GC doses are skipped, the next GC doses become Day 1/2 of the subsequent cycle. There should be at least 7 days between a skipped Day 8/9 dose and the start of the next cycle, i.e., Day 1/2. Note that the criteria for starting Day 1/2 outlined above will now apply to resumption of dosing.

After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the CCI; the Post-Treatment Visit (Day 22); the safety follow-up

phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study, which is to continue until at least 50% of patients have died.

The G1T28-04 study will be completed when the Survival Follow-up Phase has been completed, or upon sponsor termination of the study. The total study duration is at least 19 months, assuming 12 months of accrual, 4 weeks of screening, 4.5 months of treatment (assuming 6 cycles), and 2 months of safety follow-up.

The study scheduled assessments are presented in Table 2 and Table 3 below:

Table 2 Schedule of Assessments for Groups 1 and 2

	Screening	Cycle 1 and Every Odd Cycle[a] (21 days)			Cycle 2 and Every Even Cycle[a] (21 days)			Post-Treatment Visit[b]	Safety Follow-up Phone Call[c]	Survival Follow-up[d]	Post-Treatment Visit + 60 days
Cycle Day	**-28**	**1**	**8**	**15 (±1 day)**	**1**	**8**	**15 (±1 day)**	**22 (last cycle) (+7 days)**	**(+3 days)**	**(±7 days)**	**(±7 days)**
Informed Consent	X										
Demographics	X										
Medical History[e]	X										
Eligibility Evaluation	X										
Performance Status	X	X			X			X			
Physical Exam	X	X			X			X			
Vital Signs	X	X[f]	X[f]		X[f]	X[f]		X			
Height/Weight	X[g]	X			X[g1]						
Clinical Chemistry	X	X[h]			X[h]			X			
Hematology[i]	X	X	X	X	X	X	X	X			X
Urinalysis	X										
ECG	X	X[j]									
Pregnancy test[k]	X	X[k]						X			
CCI											
Tumor Assessment	X[m, m1,m2]	CT/MRI of chest/abdomen Q9 weeks through Week 27 and Q12 weeks thereafter. Also include brain MRI if brain metastases present at baseline. Skeletal lesions identified with baseline bone scan to be followed at scheduled visits using localized CT, MRI, or x-ray [m, m1, m2, m3,m4]							Tumor assessment Q12 weeks to continue in Post-Treatment/Follow-up only if patient discontinues study treatment for reason other than PD and has not initiated subsequent anticancer therapy[m,m4]			
Archival Tumor Tissue	X										
PK[n] (optional)		X[n]									
Trilaciclib[o]		X	X		X	X					
GC therapy[p]		X	X		X	X					
CCI											
Survival Contact[s]										X	
AEs[t]	X										
Con. Medications	X										

AE = adverse event; ECG = 12-lead electrocardiogram; CT = Computed Tomography; CCI [redacted]; MRI = Magnetic Resonance Imaging; CCI [redacted];
PK = pharmacokinetics, GC therapy= Gemcitabine and Carboplatin therapy; PD = progressive disease

a Study therapy will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator.

b Patients will return to the study center for a Post-Treatment Visit on Day 22 (+ 7 days) of their last cycle.

c A safety follow-up contact will be made to each patient at 30 days after the last dose of study treatment to collect AEs and concomitant medications.

d Follow-up should be attempted and documented for each patient that is in the long term Survival Follow-up Phase at least once every 2 months. Patients will be followed for survival until at least 50% of the patients have died. Any anticancer therapies used will be collected.

e Including medical, surgical, radiation history, smoking history, prior systemic anti-cancer therapy, breast cancer history including BRCA classification, screening signs and symptoms within 4 weeks prior to randomization, and medications. Eligibility evaluation and randomization may occur up to 4 days prior to Day 1 Cycle 1 therapy. For all treatment groups, study start is on Cycle 1 Day 1.

f Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be obtained immediately before and after each infusion. Vitals only need to be taken once between each infusion.

g Height will only be measured at the screening visit. Body Surface Area (BSA) will be calculated at Day 1.

g1: BSA (based on actual body weight) will be re-calculated on Day 1 of Cycle 2 and subsequent cycles if weight increases or decreases > 10% from Day 1 of the previous cycle.

h Clinical chemistry (see Protocol Section 11.4.2) may be obtained up to 72 hours prior to Day 1 of each cycle.

i Hematology (see Protocol Section 11.4.2) may be obtained up to 24 hours prior to dosing on Days 1 and 8 of each cycle, Day 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

j Single 12-lead ECGs will be obtained for all patients at screening. For those patients (Groups 1 and 2) who agree to participate in PK sampling will have ECGs completed in triplicate (at least 1 minute apart) at the following additional time points on Day 1 of Cycle 1: predose (prior to trilaciclib) and at 0.5 hour (end of infusion [EOI] of trilaciclib), 2 hours (± 10 minutes) after EOI of trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib. Patients should rest for approximately 5 minutes prior to each ECG assessment. The ECGs should be obtained just prior to PK sampling.

k Female patients of childbearing potential: serum ß-hCG at screening and serum or urine ß-hCG on Day 1 of Cycle 1, Day 1 of every odd cycle, and at the Post-Treatment Visit. A pregnancy test should be obtained within 24 hours of the Cycle 1 Day 1 visit and must be negative to initiate treatment.

CCI [redacted]

m For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI with contrast, where clinically possible, of the chest and abdomen at screening (unless obtained within 28 days of dosing), every 9 weeks ± 7 days (Week 9, Week 18 and Week 27) and then every 12 weeks ± 7 days thereafter, until the occurrence of disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion. If a patient shows a radiological response (complete response [CR] or partial response [PR]), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography is used, it should also be accompanied by spiral CT or MRI.

m1: Radionuclide bone scans shall be performed at screening. Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI or x-ray. Bone scans need not be repeated after baseline unless clinically indicated. Bone scans obtained as standard of care prior to screening will not need to be repeated if performed within 28 days prior to the first dose of study drug(s).

m2. Brain imaging with contrast (by CT or MRI) performed at Screening for all patients. If brain metastases are present at screening, brain imaging shall be done with each protocol-specified tumor assessment. If no metastases are present at screening, imaging does not need to be performed during the study unless clinically indicated or if the subject is neurologically symptomatic.

m3: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks).

m4: For those patients in the Survival Follow-up Phase who have not progressed at the time of study drug discontinuation, radiological tumor assessments will be performed utilizing the same imaging modality used at screening, every 12 weeks ± 7 days from the Post-Treatment Visit until the occurrence of progressive disease, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion.

n Patients who have agreed to participate in the PK analysis will have blood samples collected on Day 1 of Cycle 1 only at the time points specified in Section **Error! Reference source not found.**. **The end of infusion (EOI) sample for trilaciclib should be drawn 2 to 5 minutes prior to the trilaciclib EOI.**

o For Group 2: Trilaciclib will be administered as an IV infusion over 30 (±5) minutes prior to GC chemotherapy on Days 1 and 8 of every 21-day cycle (dosing information, see Protocol Section 8.1). After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO scales; the Post-Treatment Visit (Day 22); the safety follow-up phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study.

p For Group 1: GC therapy will be administered as an IV infusion on Days 1 and 8 of 21-day cycles (dosing information; see Protocol Section 8.1).

For Group 2: GC therapy will be administered as an IV infusion after the trilaciclib infusion (with an interval not greater than 4 hours) on Days 1 and 8 of 21-day cycles (dosing information; see Protocol Section 8.1). Chemotherapy cannot be administered until after completion of the trilaciclib infusion. If trilaciclib in any given cycle is not administered for any reason, do not administer the dose of gemcitabine or carboplatin chemotherapy on that day.

CCI [redacted]

s Survival follow-up may be a phone contact if subject is not returning to the clinic for tumor assessments.

t AEs will be recorded from the time of informed consent. All AEs should be reported within 30 days of the last dose of study drug, and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

Table 3 Schedule of Assessments for Group 3

	Screen-ing	Cycle 1 and Every Odd Cycle[a] (21 days)					Cycle 2 and Every Even Cycle[a] (21 days)					Post-Treatment Visit[b]	Safety Follow-up Phone Call[c]	Survival Follow-up[d]	Post-Treatment Visit + 60 days
Cycle Day	**-28**	**1**	**2**	**8**	**9**	**15 (±1 day)**	**1**	**2**	**8**	**9**	**15 (±1 day)**	**22 (last cycle) (+7 days)**	**(+3 days)**	**(±7 days)**	**(±7 days)**
Informed Consent	X														
Demographics	X														
Medical History[e]	X														
Eligibility Evaluation	X														
Performance Status	X	X					X					X			
Physical Exam	X	X					X					X			
Vital Signs	X	X[f]	X[f]	X[f]	X[f]		X[f]	X[f]	X[f]	X[f]		X			
Height/Weight	X[g]	X					X[g,l]								
Clinical Chemistry	X	X[h]					X[h]					X			
Hematology[i]	X	X		X		X	X		X		X	X			X
Urinalysis	X														
ECG	X		X[j]												
Pregnancy test[k]	X	X[k]										X			
CCI															
Tumor Assessment	X[m,m1,m2]	CT/MRI of chest/abdomen Q9 weeks through Week 27 and Q12 weeks thereafter. Also include brain MRI if brain metastases present at baseline. Skeletal lesions identified with baseline bone scan to be followed at scheduled visits using localized CT, MRI, or x-ray [m, m1, m2, m3, m4]											Tumor assessment Q12 weeks to continue in Post-Treatment/Follow-up only if patient discontinues study treatment for reason other than PD and has not initiated subsequent anticancer therapy[m,m4]			
Archival Tumor Tissue	X														
PK[n] (optional)			X												
Trilaciclib[o]		X	X	X	X		X	X	X	X					
GC therapy[p]			X		X			X		X					
CCI															
Survival contact[s]														X	
AEs[t]	X														
Con. Medications	X														

AE = adverse event; ECG = 12-lead electrocardiogram; CT = Computed Tomography; CCI [redacted] t; MRI = Magnetic Resonance Imaging; CCI [redacted] ;
PK = pharmacokinetics, GC therapy= Gemcitabine and Carboplatin therapy; PD = progressive disease

a Study therapy will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator.

b Patients will return to the study center for a Post-Treatment Visit on Day 22 (+ 7 days) of their last cycle.

c A safety follow-up contact will be made to each patient at 30 days after the last dose of study treatment to collect AEs and concomitant medications.

d Follow-up should be attempted and documented for each patient that is in the long term Survival Follow-up Phase at least once every 2 months. Patients will be followed for survival until at least 50% of the patients have died. Any anticancer therapies used will be collected.

e Including medical, surgical, radiation history, smoking history, prior systemic anti-cancer therapy, breast cancer history including BRCA classification, documentation of tumor diagnosis, screening signs and symptoms within 4 weeks prior to randomization, and medications. Eligibility evaluation and randomization may occur up to 4 days prior to Day 1 Cycle 1 therapy. For all treatment groups, study start is on Cycle 1 Day 1.

f Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be obtained immediately before and after each infusion. Vitals only need to be taken once between each infusion.

g Height will only be measured at the screening visit. Body Surface Area (BSA) will be calculated at Day 1.

g1: BSA (based on actual body weight) will be re-calculated on Day 1 of Cycle 2 and subsequent cycles if weight increases or decreases >10% from Day 1 of the previous cycle.

h Clinical chemistry (see Protocol Section 11.4.2) may be obtained up to 72 hours prior to Day 1 of each cycle.

i Hematology (see Protocol Section 11.4.2) may be obtained up to 24 hours prior to GC dosing of on Day 2 or Day 9 of each cycle, Day 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

j Single 12-lead ECGs will be obtained for all patients at screening. Those patients who agree to participate in **PK sampling** will have ECGs completed in triplicate (at least 1 minute apart) at the following additional time points on Day 2 of Cycle 1: predose (prior to trilaciclib) and at 0.5 hour (end of infusion [EOI] of trilaciclib), 2 hours (± 10 minutes) after EOI of trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib. Patients should rest for approximately 5 minutes prior to each ECG assessment. The ECGs should be obtained just prior to PK sampling.

k Female patients of childbearing potential: serum ß-hCG at screening and serum or urine ß-hCG on Day 1 of Cycle 1, Day 1 of every odd cycle, and at the Post-Treatment Visit. A pregnancy test should be performed within 24 hours of the Cycle 1 Day 1 visit and must be negative to initiate treatment.

CCI [redacted]

m For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI with contrast, where clinically possible, of the chest and abdomen at screening (unless obtained within 28 days of dosing) every 9 weeks ± 7 days (Week 9, Week 18, and Week 27) and then every 12 weeks ± 7 days thereafter, until the occurrence of disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion. If a patient shows a radiological response (complete response [CR] or partial response [PR]), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography is used, it should also be accompanied by spiral CT or MRI.

m1: Radionuclide bone scans shall be performed at screening. Bone scans obtained as standard of care prior to screening will not need to be repeated if performed within 28 days prior to the first dose of study drug(s). Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI, or x-ray. Bone scans need not be repeated after baseline unless clinically indicated.

m2: Brain imaging with contrast (by CT or MRI) performed at Screening for all patients. If brain metastases are present at screening, brain imaging shall be done with each protocol-specified tumor assessment. If no metastases are present at screening, imaging does not need to be performed during the study unless clinically indicated or if the subject is neurologically symptomatic.

m3: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks).

m4: For those patients in the Survival Follow-up Phase who have not progressed at the time of study drug discontinuation, radiological tumor assessments will be performed utilizing the same imaging modality as used at screening, every 12 weeks ± 7 days from the Post-Treatment Visit until the occurrence of progressive disease, withdrawal of consent, initiation of anticancer therapy, or study completion.

n Patients who agree to participate in the PK analysis will have blood samples collected on Day 2 of Cycle 1 at the time points specified in Protocol Section 11.4.2. **The end of infusion (EOI) sample for trilaciclib should be drawn 2 to 5 minutes prior to the trilaciclib EOI.**

o For Group 3: trilaciclib will be administered as an IV infusion over 30 (±5) minutes on Days 1, 2, 8, and 9 of every 21-day cycle. Trilaciclib will be administered prior to GC on Days 2 and 9 (dosing information, see Protocol Section 8.1). The interval between doses of trilaciclib on successive days should not be greater than 28 hours. After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO scales; the Post-Treatment Visit (Day 22); the safety follow-up phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study.

p For Group 3: GC therapy will be administered as an IV infusion after the trilaciclib infusion (with an interval not greater than 4 hours) on Days 2 and 9 of 21-day cycles (dosing information; see Protocol Section 8.1). Chemotherapy cannot be administered until after completion of the trilaciclib infusion. If trilaciclib in any given cycle is not administered for any reason, do not administer the dose of gemcitabine or carboplatin chemotherapy on that day.

CCI [redacted]

s Survival follow-up may be a phone contact if subject is not returning to the clinic for tumor assessments.

t AEs will be recorded from the time of informed consent. All AEs should be reported within 30 days of the last dose of study drug, and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

2.3. Number of Patients

Overall, approximately 90 patients will be enrolled in the study. The 90 patients will be randomly assigned (1:1:1) to 1 of 3 groups.

The sample size is not determined from a statistical perspective, but rather is based on clinical feasibility. Approximately 90 patients will be enrolled into the study (30 per treatment group). With 30 patients, the precision for point estimates in each arm is as follows: the maximum 95% confidence interval (CI) width for binary endpoints based on Wilson score intervals is the observed proportion +/- 0.167. The 95% CI width for continuous endpoints using the t-distribution are the observed mean +/- 0.373*standard deviation of the endpoint.

With the changes to the protocol detailed in this SAP, the sample size calculation is now based on demonstrating the superiority of Group 3 (GC + Trilaciclib Day 1/2 and 8/9) and Group 1 (GC therapy alone) with respect to at least one of the primary endpoints.

With the changes, the overall type I error rate is now 0.025 (1-sided) and the type II error rate used to compute sample size is 0.10 (corresponding to 90% power).

To maintain the overall type I error rate, by using the most conservative Bonferroni procedure for the 2 primary endpoints, a 1-sided individualized type I error rate 0.025/2 = 0.0125 is assigned to each outcome variable in the sample size calculation. Assuming a common standard deviation of 2.5, a true difference in the duration of severe (Grade 4) neutropenia in Cycle 1 of at least 3 days between the Group 3 and Group 1 requires, 38 evaluable patients (19 per treatment arm in Groups 1 and 3). This implies that 60 patients need to be randomized for all 3 groups assuming a 95% evaluability rate. For occurrence endpoints (occurrence of severe (Grade 4) neutropenia, assuming its proportion of 45% for Group 1, testing for an absolute reduction of 41% to 4% with Group 3 would require a sample size of at least 96 patients (32 per treatment arm in Groups 1 and 3). Assuming a 95% evaluability rate, at least 102 patients need to be randomized for all 3 groups to complete the study. Therefore, the final adjusted sample size is 102 to account for the evaluation of 2 primary endpoints. All calculations were carried out using the POWER procedure in SAS® version 9.4.

The study will be conducted at up to 50 centers in North America and Europe.

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

Data analyses will be based on the four analysis sets defined below. Analysis sets, including exclusions based on key deviations, will be reviewed and approved by G1 Therapeutics prior to the study unblinding. See Section 7 for the changes from the protocol defined analysis sets.

3.1.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set includes all randomized patients. Analyses using the ITT will be conducted on the basis of the assigned treatment. All myelopreservation efficacy analyses will be assessed using the ITT. The ITT will also be used for analyses of progression-free survival (PFS) and overall survival (OS).

3.1.2. Modified ITT Analysis Set

A modified ITT (mITT) analysis set is a subset of the ITT analysis set and will only include the ITT patients who received at least 1 dose of study drug (gemcitabine, carboplatin, or trilaciclib). Supportive sensitivity analyses will be conducted based on the mITT analysis set for primary and key secondary efficacy endpoints to evaluate the robustness of the results. Analyses using the mITT will be conducted on the basis of the assigned treatment. mITT will be used for sensitivity of select efficacy analyses.

3.1.3. Safety Analysis Set

The safety analysis set includes all enrolled patients who received at least 1 dose of study drug (gemcitabine, carboplatin, or trilaciclib). Analyses using the safety analysis set will be conducted on the basis of the actual treatment received. All safety analyses will be assessed using the safety population.

3.1.4. Per Protocol (PP) Analysis Set

The per-protocol (PP) analysis set is a subset of mITT analysis set and will include only those patients who have no key protocol deviations (as described in Section 3.2) and who received the treatment to which they were randomized. For any patients who received the wrong treatment during any part of the study, their data will be excluded from the PP analysis set. PP analysis set may be used to analyze selected endpoints to test the robustness of results.

3.1.5. Response Evaluable Analysis Set

The Response Evaluable Analysis Set will include all patients who are in the mITT, have measurable disease (target lesions) at the baseline tumor assessment, and either (i) have at least 1 post-baseline tumor assessment, (ii) have clinical progression as noted by the investigator before their first post-baseline tumor scan, or (iii) have died due to disease progression before their first post-baseline tumor scan. The response evaluable analysis set will be used for sensitivity analyses of tumor response.

3.2. Protocol Deviations

Certain protocol deviations are key in that they may affect the ability to assess the safety and efficacy of study drug. Patients with key deviations will be excluded from the PP analysis set.

All patients who meet the definition of the ITT/mITT analysis sets will be included in the ITT/mITT analysis set regardless of these deviations.

The criteria for inclusion in the PP set will be finalized and documented prior to locking data for the study.

If a patient is randomized, but fails to receive treatment, the reason for not receiving treatment will be noted in the CSR. Any such patients who are not treated will be excluded from the mITT, safety, response evaluable, and PP analysis sets but will be included in the ITT and in the patient listings for the CSR.

If the wrong treatment is administered to a patient, and the reason for the incorrect treatment is documented, this will be noted in the CSR and the patient's data included in the Safety Analysis Set based on the actual treatment received. Additional protocol deviations will be reviewed in a data review meeting to classify protocol deviations as non-key or key, and to discuss the potential impact on statistical analysis.

4. PROSPECTIVELY DEFINED ANALYSES

As outlined in the protocol, trilaciclib is an IV cyclin dependent kinase (CDK) 4/6 inhibitor being evaluated for its ability to decrease chemotherapy-induced myelosuppression when administered in combination with cytotoxic chemotherapy. Unlike granulocyte-colony stimulating factor (GCSF), which stimulates production of neutrophils, and transfusions, which only replace red blood cell (RBC) or platelets, trilaciclib is hypothesized to facilitate myelopreservation of all hematopoietic lineages including neutrophils, RBC, platelets, lymphocytes, etc.

Based on the mechanism of action, it is also hypothesized that the effects of trilaciclib-induced myelopreservation may be more obvious after patients receive repeated cycles of chemotherapy. For example, TNBC patients treated with gemcitabine and carboplatin often have more dosing reductions and hematologic-related adverse events (AEs) after multiple cycles due to repeated damage to the bone marrow. In contrast, addition of trilaciclib to gemcitabine and carboplatin is theorized to counteract the chemotherapy-induced damage and allow patients to receive multiple cycles of therapy with less dose reductions and fewer hematologic-related AEs.

To capture these two aspects of trilaciclib benefit, the following analyses are prospectively proposed in Table 4 and their associated endpoint derivation and analysis methods will be detailed in Sections 5.1 and 6.2.7 with the multiplicity adjustments described in Section 6.2.7.1.3.

Table 4 Prospectively Defined Analyses

Occurrence (proportion of patients) of severe (Grade 4) neutropenia
Duration of severe (Grade 4) neutropenia
Occurrence (proportion of patients) of RBC transfusions on/after 5 weeks
Occurrence (proportion of patients) of GCSF administration
Occurrence (proportion of patients) of Platelet transfusion
Cumulative incidence of major adverse hematologic events (MAHE) which is defined to include components as the following: • All-cause hospitalizations • All-cause dose reductions • Febrile neutropenia • Prolonged severe (Grade 4) neutropenia (duration > 5 days) • RBC transfusions on/after 5 weeks • Platelet transfusions
All-cause hospitalizations in the MAHE composite
All-cause dose reductions in the MAHE composite
Febrile neutropenia in the MAHE composite
Prolonged severe (Grade 4) neutropenia in the MAHE composite
RBC transfusions on/after 5 weeks in the MAHE composite
Platelet transfusions in the MAHE composite

RBC = Red Blood Cell; GCSF = granulocyte-colony stimulating factor;

5. PRIMARY AND SECONDARY ENDPOINTS

The following general definitions will be applied to all endpoints derivation unless otherwise specified.

Term	Definition
Severe Neutropenia (SVN)	ANC lab value that meets the common terminology criteria for adverse events (CTCAE) criteria for ≥ Grade 4 toxicity
Cycle baseline	The last non-missing value within the window starting from 3 days prior to the date/time of study drug administration on Day 1 of Cycle 1 and 1 day prior to Day 1 of each subsequent cycle (i.e. Cycle 2, Cycle 3, etc.); must be prior to the time of study drug administration
Cycle nadir	The lowest value for a given hematologic parameter that occurs between start of cycle and end of cycle and is less than the cycle baseline.
Duration of cycle	Total number of days from start of cycle to end of cycle, that is, date of end of a cycle - date of start of cycle + 1.
End of cycle*	Day 1 of the subsequent cycle. For example, the end of cycle for Cycle 1 is Day 1 of Cycle 2. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as Day 30 after the first dose of the cycle.
Start of cycle	Day 1 of each cycle starts with the administration of study drug(s) (gemcitabine, carboplatin or trilaciclib)
Start of study	Date of randomization
Study baseline	The last non-missing value prior to, or on the date of administration of study drug(s) (gemcitabine, carboplatin or trilaciclib); must be prior to the time of study drug administration
Change from baseline	Calculated as the post-baseline value minus the baseline value. If the baseline value is missing for a particular endpoint, change from baseline will be missing.
Treatment period	Between the date of randomization and end of cycle for the last cycle

* For various hematologic parameter analyses, the last assessment prior to end of cycle will be utilized in the analyses. Situations where this applies will be indicated as such.

5.1. Efficacy Endpoints

5.1.1. Primary Endpoints

5.1.1.1. Occurrence of Severe (Grade 4) Neutropenia

For the treatment period, the total number of SVN events is the number of cycles where at least one ANC value is $< 0.5 \times 10^9$/L. For example, if Cycle 2 has two ANC values that are both $< 0.5 \times 10^9$/L, this only counts as one event. If a patient did not have any SVN events, the value of 0 will be assigned to that patient. Unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation.

Hence, any occurrence of an SVN during the treatment period is defined as a binary variable (Yes or No); Yes, if total number of cycles with SVN ≥ 1 is observed, No for other scenarios.

5.1.1.2. Duration of Severe (Grade 4) Neutropenia (DSN)

There will be two different strategies for assessing DSN in each cycle. Both strategies will be applied to derive the DSN, with strategy 1 considered as the primary, and strategy 2 being supportive sensitivity analyses. The DSN in Cycle 1 is considered for this primary endpoint.

5.1.1.2.1 Strategy 1: Without Imputation of Missing ANC Values

Within each cycle, the DSN (days) is defined as the number of days from the date of first ANC value of $<0.5\times10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5\times10^9$/L that meets the following criteria: (1) occurs after the ANC value of $<0.5\times10^9$/L and (2) no other ANC values $<0.5\times10^9$/L occur between this day and end of cycle. DSN is set to 0 in patients who did not experience SVN in a cycle. Any unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation. The following rules will be applied in the calculation:

(i) For a cycle where the SVN event does not resolve by end of the cycle, DSN will be assigned as above except the end date will be the end of cycle.

(ii) For a cycle where the patient dies, during the SVN event, DSN will be assigned as above except the end date will be the date of death.

(iii) For a cycle where the patient withdraws consent or is lost to follow-up during the SVN event, DSN will be assigned as above except the end date will be the date of the last ANC assessment prior to the end of study.

5.1.1.2.2 Strategy 2: Without Imputation, Censoring Unresolved SVN

Within each cycle, DSN (days) is defined as the number of days from the date of first ANC value of $<0.5 \times 10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5 \times 10^9$/L that meets the following criteria: (1) occurs after the ANC value of $<0.5 \times 10^9$/L and (2) no other ANC values $<0.5 \times 10^9$/L occur between this day and end of cycle. The following censoring rules will be applied in the calculation:

(iv) For a cycle where the SVN event does not resolve by end of the cycle, DSN will be assigned as above except the end date will be the earlier of end of cycle or date of last contact.

(v) For a cycle where the patient dies, withdraws consent, or is lost to follow-up during the SVN event, DSN will be assigned as above except the end date will be the date of the last ANC assessment prior to the end of study.

For the treatment period, the overall DSN (days) is the median value among the DSN (days) from all cycles. The following data handling conventions will apply:

- For those patients where all event duration values are derived from cycles with censored data, the median value for that patient will be the median censored value. It will be a considered a censored value;
- For those patients where a subset of event duration values are derived from cycles with censored data, the median value for that patient will be estimated using the Kaplan-Meier method. It will be considered as an observed value (i.e. no censored value);

- For those patients where the median event duration cannot be derived (e.g. ≤ 2 values), the longest event duration amongst all the cycles will be used regardless of censoring, but the corresponding censoring flag will be carried over for analysis.

5.1.2. Key Secondary Endpoints

5.1.2.1. Occurrence of RBC Transfusions

Each RBC transfusion with a unique start date on/after 5 weeks on study during the treatment period will be defined as a separate event, and an additional set of all events occurring during the treatment period will be examined for sensitivity.

Occurrence of a RBC transfusion during the treatment period is defined as a binary variable (Yes or No); Yes if total number of RBC transfusion ≥ 1 is observed, No for other scenarios.

5.1.2.2. Occurrence of GCSF Administrations

Administration of GCSF is collected throughout the treatment period. Those cycles where GCSF is administered concurrently will be identified by comparing the start and stop dates of each administration of GCSF to the start of cycle and end of cycle. If any of the dates of administration of GCSF overlap with any dates between the start of cycle and end of cycle, that cycle will be considered as having GCSF administered. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

For the treatment period, the total number GCSF administrations is the number of cycles in which there is at least one GCSF dose administered. If a patient did not have any GCSF use, the value of 0 will be assigned to that patient. The number of cycles where GCSF was NOT given is calculated as total number of treatment cycles received – total number of cycles where GCSF was administered.

Therefore, any occurrence of a GCSF administration during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with GCSF administration ≥ 1 is observed, No for other scenarios.

5.1.2.3. Occurrence of Platelet Transfusions

Each platelet transfusion with a unique start date during the treatment period will be defined as separate event.

Occurrence of a platelet transfusion during the treatment period is defined as a binary variable (Yes or No); Yes if total number of platelet transfusion ≥ 1 is observed, No for other scenarios.

5.1.2.4. Total Number of Major Adverse Hematologic Events (MAHE)

As a composite measure of trilaciclib effect, MAHE is based on a combination of individual components specified in Table 5, which also include details about the derivation or data source for each component. For each component of composite MAHE, its number of events is derived as the number of episodes with a unique start date during the treatment period between the date of randomization and the end of the last cycle (i.e. last cycle of GC only or trilaciclib plus GC). A patient with absence of an episode will be assigned a value of 0 to the number of events for this component. Then, the total number of MAHE during the treatment period is obtained as the summation over all components of composite MAHE during the treatment period.

Table 5 Component of MAHE and the Suggested Data Source/Derivation Algorithm

Seq #	Component of MAHE	Details
1	All-cause hospitalizations	Each hospitalization is captured in the AE data of the electronic database. Each recorded Preferred Term (PT) with a unique start date will be counted as an event. The event terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.
2	All-cause dose reductions	Detailed in Section 5.1.2.4.2**Error! Reference source not found.**
3	Febrile neutropenia	Detailed in Section 5.1.3.8**Error! Reference source not found.**
4	Prolonged severe (Grade 4) neutropenia (duration > 5 days)	Detailed in Section 5.1.1.2.1. Each cycle with a duration greater than 5 days will be counted as an event with the date of the first grade 4 lab value defined as the start date for the time-to-first event analysis.
5	RBC transfusion on/after 5 weeks	Detailed in Section 5.1.2.1
6	Platelet transfusion	Detailed in Section 5.1.2.3.

A patient with absence of any episode of MAHE will be assigned a value of 0 for the total number of MAHE. Additionally, a sensitivity analysis will be done for dose reductions and RBC transfusions on/after 5 weeks, that excludes patients who do not start a second cycle of treatment.

Time to first occurrence of a MAHE will be used as a sensitivity analysis in support of the total number of MAHE. It is defined as the first time to observe an event among all the components, starting from the date of randomization. Therefore, for a patient with presence of MAHE, time (months) to first occurrence of a MAHE will be the minimum among the 6 potentially derived duration (i.e. calculated as (date of first occurrence of a MAHE component event – date of randomization + 1)/30). A patient without any MAHE will be censored at the end of the last cycle (i.e. last cycle of GC only or trilaciclib plus GC), death, end of study, or date of last contact, whichever is earlier.

5.1.2.4.1 All-Cause Hospitalizations

See Section 5.1.2.4.

5.1.2.4.2 Occurrence of All-Cause Dose Reductions

Dose (mg/m^2) reductions are not permitted for trilaciclib. Dose reductions for carboplatin and gemcitabine are derived from changes in the planned dose on the dosing page.

Up to 3 total dose reductions are allowed for carboplatin and gemcitabine, each will be counted as a unique event. For more details see Section 5.2.1.4.

5.1.2.4.3 Prolonged severe (Grade 4) neutropenia (duration > 5 days)

See Section 5.1.2.4.

5.1.3. Supportive Secondary Endpoints

5.1.3.1. Best Overall Response, Duration of Response, Progression-Free Survival, and Overall Survival

For tumor assessment, all sites of disease will be assessed radiologically by CT or MRI at screening, every 6-12 weeks thereafter as determined by the protocol, until the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. At each tumor assessment visit, the overall visit response by RECIST will be determined two ways: (1) derived programmatically using the information from target lesions (TL), non-target lesions (NTLs) and new lesions as entered into the eCRF, and (2) by the investigator and collected in the eCRF.

For all patients, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST Version 1.1 and the best overall response (BOR).

5.1.3.1.1 Target Lesions (TLs)

Measurable disease is defined as having at least one measurable lesion which is

- ≥10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI); or
- ≥10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); or
- ≥ 20 mm by chest X-ray.

Previously irradiated lesions (or lesions treated with loco-regional therapies) may be considered measurable if unequivocal growth of the lesion has been demonstrated. A patient can have a maximum of 5 measurable lesions representative of all involved organs (maximum of 2 lesions per organ, both the lymph node and skin will be considered as a single organ) recorded at baseline and these are referred to as target lesions. If more than one baseline scan is recorded then measurements from the one that is closest to start of treatment will be used to define the baseline sum of TLs. Table 6 gives definition of TL visit responses.

Table 6 Definition of TL Visit Responses

Visit Reponses	Description
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of target lesions and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters (i.e. nadir) since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a target lesion response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

If any target lesion measurements are missing then the target lesion visit response is Not Evaluable (NE). The overall visit response will also be NE, unless there is a progression of non-target lesions or new lesions, in which case the response will be PD.

TL too small to measure

If a target lesion becomes too small to measure a value of 5mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured.

Lesions that split

If a TL splits, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If target lesions merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 cm.

Change in method of assessment of target lesions

CT, MRI, chest x-ray and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination and, chest x-ray only used in special cases. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

5.1.3.1.2 Non-Target Lesions (NTLs) and New Lesions

The non-target lesion response will be based on the Investigator's assessment of NTLs as Table 7:

Table 7 Definition of NTLs Visit Responses

Visit Reponses	Description
CR	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10mm short axis).
PD	Unequivocal progression of existing NTLs, which may be due to an important progression in one lesion only or in several lesions
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression
NE	Only relevant when one or some of the NTLs have not been assessed and in the Investigator's opinion they are not able to provide an evaluable overall NTL assessment.

New lesions

New lesions will be identified via a separate eCRF page. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression, so the overall visit response will be PD irrespective of the TL and NTL responses.

5.1.3.1.3 Time Point Response (TPR)

Table 8 and Table 9 define how the previously defined TL and NTL visit responses will be combined with new lesion information to give a TPR. The possible TPRs at a visit are CR, PR, SD, Non-CR/Non-PD, PD, and NE.

Table 8 Evaluation of Time Point Response: Patients with Baseline Target Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/not all evaluated	No	PR
SD	Non-PD/not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

Table 9 Evaluation of Time Point Response: Patients without Baseline Target Lesions

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

At each visit, patients will be programmatically assigned a RECIST Version 1.1 TPR of CR, PR, SD, Non-CR/Non-PD, PD or NE depending on the status of their disease compared to baseline and previous assessments as discussed in the Sections 5.1.3.1.1 and 5.1.3.1.2.

For a scheduled tumor scan assessment, it is expected that there will be a variation for the actual timing of scans among target, non-target, and new lesions. In assigning a date for the derived overall assessment at a visit, the earliest date collected at that visit will be used. Within a grouped timepoint, if there are multiple assessments on different dates for the *same* target lesions, the last assessment will be used.

5.1.3.1.4 Best Overall Response (BOR) and Duration of Response (DOR)

BOR will be determined using TPRs up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. BOR will not be derived for those patients who do not have measurable target lesions.

A patient's BOR will be determined based on Table 10. For data-driven scenarios which may not be covered by Table 10, the BOR will be reviewed and determined by the medical advisors and statisticians prior to locking the database.

For patients who progress and subsequently have a response, the best overall response is only derived from assessments up to and including the time of the progression (i.e., it will not include the response after the patient has progressed).

There are two ways of assigning BOR for a patient when the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR:

- Adding two more response categories as: unconfirmed CR, unconfirmed PR;
- Assigning BOR as SD, that is, both the unconfirmed CR and unconfirmed PR will be SD.

Both ways of assigning BOR will be implemented.

The number and percentage of patients in each category of derived BOR (Confirmed CR, Confirmed PR, SD, PD, or NE) will be summarized.

Table 10 Best Overall Response When Confirmation of CR and PR are Required [a]

First TPR	Second TPR	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	CR	CR	CR
CR	PR	SD [b] or PD	Unconfirmed CR
CR	SD	SD [b] or PD	Unconfirmed CR
CR	PD	SD [b] or PD	Unconfirmed CR
CR	NE or NA	SD [c] or NE or NA	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD [d]	Unconfirmed PR
PR	PD	SD [b] or PD	Unconfirmed PR
PR	NE or NA	SD [c] or NE or NA	Unconfirmed PR
NE	NE	NE	NE
NE	CR	SD	Unconfirmed CR
NE	PR	SD	Unconfirmed PR
NE	SD	SD	SD
NE or NA	PD	PD	PD
SD	PD	SD [b] or PD	SD [b] or PD
SD	CR	SD	SD
SD	PR	SD	SD
SD	SD	SD	SD
SD	NE or NA	SD [c] or NE or NA	SD [c] or NE
PD	No further evaluation	PD	PD
Non-CR/Non-PD	PD	PD	PD
Non-CR/Non-PD	CR	Non-CR/Non-PD	Non-CR/Non-PD
Non-CR/Non-PD	PR	Non-CR/Non-PD	Non-CR/Non-PD
Non-CR/Non-PD	SD	Non-CR/Non-PD	Non-CR/Non-PD
Non-CR/Non-PD	NE or NA	NE or NA	NE

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not available, ORR = Objective Response Rate

a. The minimum interval for confirmation of CR and PR is 4 weeks.

b. Best response will be SD if the first time point overall response is after 35 days on study. Otherwise, the best response will be PD.

c. Best response will be SD if the first time point overall response if after 35 days on study. Otherwise, the best response will be NE.

d. Best response will be SD provided the criteria for PD have not been met from the first to second assessment.

* A best overall response of SD can only be made after the subject is on study for a minimum of 35 days (counted from Cycle 1 Day 1). If the subject is on study for less than 35 days, any tumor assessment indicating stable disease before this time period will have a best response of NE unless PD is identified.

^Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE (e.g., CR NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an

intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening NE or SD will be allowed between PRs for confirmation. Note: in the following scenario, PR SD NE PR, the second PR is not a confirmation of the first PR.

Objective response rate (ORR) will be calculated using two methods:

Method #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes (0/1) variable. Patients with a BOR of confirmed CR or PR will be assigned 'Yes'. Patients not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of patients with objective response being "Yes".

Method #2: $ORR_{UNCONFIRMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes (0/1) variable. Patients with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All patients with other BOR values will be assigned "No". Hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of patients with objective response being "Yes".

Duration of Response (DOR) is the time between first response by RECIST Version 1.1 of CR or PR and the first date that progressive disease is documented by RECIST Version 1.1, or death. Patients who do not experience PD or death will be censored at the last tumor assessment date. Only those patients with confirmed responses will be included in this analysis. Censoring will follow the rules outlined below for PFS in Section 5.1.3.1.5.

Clinical benefit rate (CBR) is defined as the proportion of patients with a BOR of confirmed CR, confirmed PR, or SD.

ORR, $ORR_{UNCONFIRMED}$, DOR and CBR will be calculated using the derived responses and investigator responses.

5.1.3.1.5 Progression-free Survival

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented.

Hence, progression-free survival (PFS) is defined as the time (months) from date of randomization until date of documented disease progression or death due to any cause, whichever comes first. More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

PFS will be calculated using derived responses and progression by RECIST Version 1.1 (whichever comes first) will be considered.

Death, regardless of cause, is always considered as a PD event. The detailed censoring rules for the analysis are summarized in Table 11.

Table 11 Assignment of Progression or Censoring Based on Radiological Assessment

Situation	Date of Progression or Censoring	Outcome
No Baseline assessment	Date of randomization	Censored
No progression - treatment not started	Date of randomization	Censored
No progression	Date of last adequate radiological disease assessment	Censored
Treatment discontinuation for reasons other than disease progression	Date of last adequate radiological disease assessment with no documented progression	Censored
New anticancer treatment started prior to documented disease progression	Date of last adequate radiologic assessment no later than the initiation of new anticancer treatment	Censored
Disease progression per RECIST Version 1.1	Date of the first reported progression	Progressed
Death without a PD	Date of death	Progressed
Determination of clinical progression per the investigator	Date of the investigator assigned PD	Progressed [a]

[a] For the primary derivation of PFS, the clinical progression will not be included (i.e. it will only be based on radiologic progression), but it will be incorporated as a separate derivation of PFS, and its analysis will be considered to be supportive.
Note: An adequate radiologic assessment is defined as an assessment where the Investigator determined radiological response is CR, PR, SD, or PD. If PD and new anti-cancer therapy occur on the same day, will assume that the progression was documented first, *e.g.* outcome is progression and the date is the date of the assessment of progression.

5.1.3.1.6 Overall Survival

Overall survival is calculated as the time (months) from date of randomization to the date of death due to any cause. Patients who do not die during the study will be censored at the date last known to be alive. Patients lacking data beyond the date of randomization will have their survival time censored at date of randomization. OS will not be censored if a patient receives other anti-tumor treatments after the study drugs. The analysis of OS will be primarily aimed at showing lack of harm from trilaciclib.

5.1.3.2. Occurrence of Grade 3 and 4 Hematologic Toxicities

Hematologic toxicities events are defined as any cycle where any hematologic lab value occurs that meets the CTCAE toxicity grade criteria for ≥ Grade 3 and the value is treatment emergent. For details on which parameters are included and the definition of treatment emergent see Section 5.2.4.

For the treatment period, the total number of hematologic toxicity events is the number of cycles in which there is at least one hematologic toxicity event. If a patient did not have any

hematologic toxicity events, the value of 0 will be assigned to that patient. The number of cycles without hematologic toxicity events is calculated as total number of treatment cycles received – total number of cycles with a hematologic toxicity event.

Therefore, any occurrence of a hematologic toxicity event during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with a hematologic toxicity event ≥ 1 is observed, No for other scenarios.

5.1.3.3. ANC Nadir by Cycle

See table in Section 5 for the definition of cycle nadir.

5.1.3.4. ANC, Platelet Count, Absolute Lymphocyte Counts (ALC), and Hemoglobin Change over Time

For the hematologic parameters consisting of ANC, hemoglobin, platelet count, and ALC, the observed lab values in each windowed visit as detailed in Section 6.1.3 will be appropriately identified for further analysis.

5.1.3.5. Occurrence of Erythropoiesis Stimulating Agent (ESA) Administrations

Administration of ESAs is collected throughout the treatment period. Those cycles where ESAs are administered concurrently will be identified by comparing the start and stop dates of each ESA to the start of cycle and end of cycle. If any of the dates of administration of an ESA overlap with any dates between the start of cycle and end of cycle, that cycle will be considered as having an ESA administered. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

For the treatment period, the total number of ESA administrations is the total number of cycles in which there is at least one ESA dose administered;. If a patient did not receive an ESA, the value of 0 will be assigned to that patient. The number of cycles where ESAs were NOT given is calculated as total number of treatment cycles received – total number of cycles where ESAs were administered.

Therefore, any occurrence of an ESA administration during the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with ESA administration ≥ 1 is observed, No for other scenarios.

5.1.3.6. Occurrence of IV Antibiotic Uses

IV antibiotic administration is collected with concomitant medications which are coded using World Health Organization Drug Dictionary (WHO-DD) Version Sep2017. The criteria for identifying an IV antibiotic administration event is

- If the Therapeutic subgroup from WHO-DD Version Sep2017 (i.e. TEXT2 for CODE2) takes value “ANTIBACTERIALS FOR SYSTEMIC USE”, and
- The route of medication is “intravenous” or the route is “other” with the detailed specification as “IVPB”.

Each IV antibiotic with a unique start date during the treatment period will be defined as a separate event. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

Occurrence of an IV antibiotics administration during the treatment period is defined as a binary variable (Yes or No); Yes if total number of IV antibiotics administration ≥ 1 is observed, No for other scenarios.

5.1.3.7. Occurrence of Infection Serious Adverse Events (SAEs)

Each infection SAE is captured in the electronic database. The event terms are coded using the MedDRA Version 20.1. The criterion for identifying the proper infection SAE records is as follows: if the system organ class (SOC) from MedDRA takes value "INFECTIONS AND INFESTATIONS", and the AE is a serious event.

Each infection SAE with a unique start date during the treatment period will be defined as separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.2.

Any occurrence of an infection SAE during the treatment period is defined as a binary variable (Yes or No); Yes if total number of infection SAE events ≥ 1 is observed, No for other scenarios.

5.1.3.8. Occurrence Febrile Neutropenia

Each febrile neutropenia event is captured in AE data of electronic database, and "FEBRILE NEUTROPENIA" is a preferred term which can be used to identify the proper AE records. The event terms are coded using the MedDRA Version 20.1.

Each febrile neutropenia event with a unique start date during the treatment period will be defined as a separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.2.

Any occurrence of a febrile neutropenia event during the treatment period is defined as a binary variable (Yes or No); Yes if total number of febrile neutropenia events ≥ 1 is observed, No for other scenarios.

5.1.3.9. Occurrence of Grade 4 and Grade 3 or 4 Thrombocytopenia

Hematologic toxicities events are defined as any cycle where any hematologic lab value occurs that meets the CTCAE toxicity grade criteria for ≥ Grade 3 and the value is treatment emergent. For details on which parameters are included and the definition of treatment emergent see Section 5.2.4.

For the treatment period, the total number of hematologic toxicity events is the number of cycles in which there is at least one hematologic toxicity event. If a patient did not have any hematologic toxicity events, the value of 0 will be assigned to that patient. The number of cycles without hematologic toxicity events is calculated as total number of treatment cycles received – total number of cycles with a hematologic toxicity event.

Therefore, any occurrence of a hematologic toxicity event during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with a hematologic toxicity event ≥ 1 is observed, No for other scenarios.

CCI [redacted]

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[redacted]

5.2. Safety Endpoints

5.2.1. Chemotherapy Exposure Endpoints

5.2.1.1. Duration of Exposure

Duration of exposure (days) = First dose date of study drug from the last cycle – first dose date of study drug + 21.

5.2.1.2. Number of Cycles Received

Patients are considered to have started a cycle if they have received at least one dose of any study drug (carboplatin, gemcitabine, or trilaciclib). In addition to the numeric summary for the number of cycles, the number of cycles will be categorized as 1, 2, 3 or 4, 5 or 6, and > 6.

5.2.1.3. Dose Intensity and Cumulative Dose

Algorithms for calculating parameters relevant to the dose exposure and intensity are included in Table 12.

Table 12 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	Trilaciclib	Gemcitabine	Carboplatin
Dosing schedule per protocol	Group 2: 240 mg/m^2 IV on Days 1 and 8 of a 21-day cycle Group 3: 240 mg/m^2 IV on Days 1, 2, 8 and 9 of a 21-day cycle	Group 1 & 2: 1000 mg/m^2 IV on Days 1, 8 of a 21-day cycle Group 3: 1000 mg/m^2 IV on Days 2, 9 of a 21-day cycle	Group 1 & 2: AUC 2 IV on Days 1, 8 of a 21-day cycle Group 3: AUC 2 IV on Days 2, 9 of a 21-day cycle
Dose by cycle	Total dose administered on Days 1 and 8 (Group 2) or Days 1, 2, 8 and 9 (Group 3) (mg) /most recent BSA (m^2) [(mg/m^2)]	Total dose administered on Days 1 and 8 (Group 2) or Days 2 and 9 (Group 3) (mg)/most recent BSA (m^2) [(mg/m^2)]	Total dose administered on Days 1 and 8 (Group 2) or Days 2 and 9 (Group 3) (Prescribed AUC and actual dose in mg)
Cumulative dose	Sum of the total doses by cycle (mg/m^2) administered to a patient in the duration of exposure, i.e. total number of cycles received [(mg/m^2)]	Sum of the total doses by cycle (mg/m^2) administered to a patient in the duration of exposure, i.e. total number of cycles received [(mg/m^2)]	Sum of the total doses by cycle (AUC) administered to a patient in the duration of exposure, i.e. total number of cycles received (in total prescribed AUC)
Dose intensity	Cumulative dose (mg/m^2) / (duration of exposure / 7) [(mg/m^2/week)]	Cumulative Dose (mg/m^2) / (duration of exposure / 7) [(mg/m^2/week)]	Cumulative Dose (total prescribed AUC) / (duration of exposure / 7) [AUC/ week]
Relative dose intensity (%)	Group 2:100 * [Dose intensity (mg/m^2/week) / (480 /3 (mg/m^2/week)] Group 3: 100 * [Dose intensity (mg/m^2/week) / (960 /3 (mg/m^2/week)]	100 * [Dose intensity (mg/m^2/week) / (2000 /3 (mg/m^2/week)]	100 * [Dose intensity (AUC/week) / (4/3) (AUC/week)]
Relative Dose (%)	Group 2:100 * [Cumulative dose (mg/m^2) / (480 ×	100 * [Cumulative dose (mg/m^2) / (2000 × number of cycles (mg/m^2)]	100 * [Cumulative dose (AUC) / (4 × number of cycles (AUC)]

Parameter	Trilaciclib	Gemcitabine	Carboplatin
	number of cycles (mg/m^2)] Group 3: 100 * [Cumulative dose (mg/m^2) / (960 × number of cycles (mg/m^2)]		

AUC = area under curve; BSA = body surface area; IV = intravenous.

5.2.1.4. Modifications of Study Therapy, Including Cycle (Dose) Delay, Skipped Doses, Dose Interruptions, and Dose Reductions.

- After Cycle 1, patients need to meet pre-specified laboratory parameter criteria before initiating Cycle 2 and each subsequent cycle of chemotherapy. A "Cycle Day Status" page asking if the patient was eligible to start a new cycle at the next visit is available on Days 15, 22, 29 and 36. If the patient is unable to start a new cycle at that next visit, then the cycle is delayed (the site answers "no"), the reason entered, and the question is asked again at the next visit until the patient either starts a new cycle or discontinues treatment. For example, if a patient returns to clinic on Day 22 and is unable to start a new cycle, the site answers the Cycle Day Status page on Day 15 as "no", enters the reason, and the patient returns to clinic on Day 29 for reassessment. The reasons for delay will be summarized as the first reason collected for a cycle in the following categories: (1) Hematological toxicity, (2) Non-hematological toxicity, (3) Other. In this particular setting, the term "hematological toxicity" is used to delineate those situations where the ANC and/or platelet values were lower than the per protocol requirements. It does not include settings where the patient had some other hematologic abnormality that could have led to a dose delay per the investigator's discretion.

- To receive Day 8/9 dose of each cycle, patients need to meet pre-specified laboratory parameter criteria. If the criteria is not met, the Day 8/9 doses are skipped. This information is collected "Cycle Day Status" page at Day 8/9. For "Did the patient receive chemotherapy at this visit?" if the answer is "no" then a skipped dose is counted. Similar to Day 1/2, the ANC must be $\geq 1.0 \times 10^9$/L in order to dose. The platelet count must be $\geq 75 \times 10^9$/L (vs. $\geq 75 \times 10^9$/L at Day 1/2). The reasons for skipped dose will be the same as the reasons for delay above. If a patient skips a dose on Day 8/9, and is able to receive dose at Day 15, then a new cycle will be started then. Otherwise that cycle will be counted as both a skipped dose and a delayed dose.

- Dose (mg/m^2) reductions are not permitted for trilaciclib. Dose reductions for carboplatin and gemcitabine are determined by comparing the planned dose on the respective drug administration pages between the current cycle and the previous cycle, and occur in the following order:
    - 1st Reduction: Carboplatin dose reduced from AUC 2 to AUC 1.5
    - 2nd Reduction: Gemcitabine dose reduced from 1000 to 800 mg/m^2.
    - 3rd Reduction: Discontinuation of either Carboplatin or Gemcitabine

After the 3rd dose reduction, no further reductions are allowed, and patient will be discontinued. Dose reduction will happen only once per cycle and patients who have the dose reductions in a cycle will have the reduced dose administered for the rest of the cycle.

- Dose interruptions for all drugs are also captured on the dosing page and will be summarized for each study drug.

5.2.2. Adverse Events (AEs)

All AEs will be coded from verbatim text to PTs and grouped by SOC using the MedDRA Version 20.1. AEs will be collected from the time of signature of informed consent throughout the treatment period and up to 30 days after the last dose of study treatment. AEs are graded by investigator according to CTCAE, Version 4.03.

Any AE that started on or after the first dose of study drugs and up to the last dose + 30 days will be included as a treatment emergent AE (TEAE). AEs with an unknown/not reported onset date will also be included.

Other AE variables include drug-related AEs, AEs leading to study drug discontinuation or study withdrawal, AEs leading to death, and SAEs.

AEs with onset/end dates that are partially/completely missing will be imputed as follows:

(i) For onset date:
- If only the day part of the AE onset date is missing and occurs in the same month and year as the first dose date of study drug, the date of first dose of study drug will be used as the onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE;
- If the day and month parts of the AE onset date are missing and occur in the same year as the first dose of study drug, the date of the first dose of study drug will be used as the onset date of the AE. Otherwise, January 1st will be used to complete the onset date of the AE;
- If the AE onset date is completely missing, the date of the first dose of study drug will be used as the onset date of the AE.

(ii) For end date:
- If only the day part of the AE end date is missing, the last day of the month will be used to complete the end date of the AE;
- If the day and month parts of the AE end date are missing, December 31st will be used to complete the end date of the AE;
- If the AE end date is completely missing and the onset date of the AE occurs after the date of the first dose of study drug, the last date during the treatment period +30 days will be used as the AE end date. If the AE end date is completely missing and the onset date of the AE occurs prior to the date of the first dose of study drug the date of the first dose of study drug will be used as the AE end date.

AEs related to hematologic toxicity will be pooled based on the preferred MedDRA Version 20.1. Table 13 outlines those terms that will be consolidated.

Table 13 Preferred Terms to Be Consolidated

Presented term in the table	Preferred Term
Neutropenia	Neutropenia
	Neutrophil count decreased
Febrile neutropenia	Febrile neutropenia
Anaemia	Anaemia
	Anaemia macrocytic
	Red blood cell count decreased
	Hemoglobin decreased
Thrombocytopenia	Thrombocytopenia
	Platelet count decreased
Lymphopenia	Lymphopenia
	Lymphocyte count decreased
Leukopenia	Leukopenia
	White blood cell count decreased

Infusion reaction AEs are signified in the study drug administration forms and that information is linked to the details entered on the AE page to distinguish those for a subset summary. Additionally, a summary from the AE data only will be presented for those records where "INFUSION RELATED REACTION" is a preferred term. The event terms are coded using the MedDRA Version 20.1.

5.2.3. Vital Signs

Vital signs include pulse rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height (only measured at screening), and body temperature. Body Mass Index (BMI) will be computed as weight (kg)/[height (m)]^2, Body Surface Area (BSA) will be computed using DuBois-DuBois formula as $0.20247 \times [\text{height (m)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated. Vitals will be summarized by visit as collected and not windowed.

The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 14:

Table 14 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Parameter	Criterion value	Change from baseline
SBP	≥180 mmHg	Increase ≥40 mmHg
	≤ 90 mmHg	Decrease ≥40 mmHg
DBP	≥105 mmHg	Increase ≥20 mmHg
	≤ 50 mmHg	Decrease ≥20 mmHg
Pulse	≥ 120 bpm	Increase ≥40 bpm
	≤ 50 bpm	Decrease ≥40 bpm

Weight	n/a	Change ≥10%

bpm = beats per minute

5.2.4. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 15 will be measured.

Table 15 Laboratory Assessment

Lab Category	Lab tests
Hematology	hemoglobin, hematocrit, white blood cell (WBC), platelet counts, ANC, ALC, Monocyte Absolute, Basophil Absolute, Eosinophil Absolute, and other non-protocol specified tests
Chemistry	albumin, Alkaline Phosphatase (ALP), total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), sodium, and Blood Urea Nitrogen (BUN), and other non-protocol specified tests
Urinalysis	semiquantitative dipstick: specific gravity, pH, evaluation of glucose, protein, bilirubin, ketones, leukocytes, and hemoglobin microscopic examination, including RBC, WBC, and casts will be performed, if necessary

Change from baseline in laboratory test results to each assessment will be calculated; for hematology parameters, the change from cycle baseline will also be obtained. The urinalysis results will not be summarized; they will only be included in listings.

Clinical laboratory results will be graded according to CTCAE criteria, Version 4.03 which can be found in Table A-1 of Appendix. Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. Any assessment for which CTCAE toxicity grades are not available, will not be included in any analyses for which toxicity grades are required.

Analysis of Abnormal Hepatic Laboratory Values

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- ALT and/or AST >3x ULN, ALP < 2xULN, and Total Bilirubin> 2x ULN
- AST > 3,5,8,10, and 20x ULN, AST>5x ULN for more than 5 weeks
- ALT > 3,5,8,10, and 20x ULN, ALT > 5x ULN for more than 5 weeks
- Total Bilirubin >1.5 or >2x ULN

5.2.5. Electrocardiograms

Electrocardiogram (ECG) parameters include heart rate, PR interval, RR interval, and QT, QTcB, QTcF and QRS intervals. Change from baseline to each post-baseline visit will be calculated and summarized by visit as collected and not windowed. Visits and timepoints only collected for PK subjects will be listed but not summarized.

Collected QTcB and QTcF will not be used, but will instead be derived from the QT and RR (converted from collected msec to sec) interval based on the following formulas:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

If QT and/or RR is missing, the QTcB and QTcF will be left as missing.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 16. ECG results are interpreted as clinically significant or not clinically significant.

Table 16 Potentially Clinically Significant Criteria for ECG

ECG Parameter	Criterion value
Heart Rate	>120 bpm
	<50 bpm
PR Interval	≥ 210ms
RR Interval	> 1200ms
	< 500ms
QRS Interval	≥ 120ms
	≤ 50ms
QT Interval	≥ 500ms
	≤ 300ms
QTcB, QTcF Intervals	≥ 500ms
	≥ 480ms
	≥ 450ms
	≤ 300ms
	Change from baseline ≥ 30 ms
	Change from baseline ≥ 60 ms

5.2.6. Physical Examination

Physical examination is conducted during screening, on Day 1 of each cycle, Day 22 (and subsequent visits if applicable) at each cycle, and at the post-treatment visit. Abnormal findings in PE were to be reported as AEs. These data will not be summarized, i.e. they will only be available in listings.

6. ANALYSIS METHODS

6.1. General Principles of Analysis

6.1.1. General Methodology

In general, all efficacy, safety and PK variables will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean, standard deviation, minimum, median, and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages). For PK variables, the geometric mean and coefficient of variation (CV) will be used instead of the arithmetic mean and standard deviation, if appropriate. Time to event variables will be analyzed with Kaplan-Meier method and summarized with median, twenty-fifth and seventy-fifth percentiles, and 95% confidence intervals (CI), if applicable. Individual data will be presented in patient listings.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e. ICH-E3, will be used for all tables and listings. Upon completion, all SAS® programs will be validated by an independent programmer within the staff of the third-party vendor doing the primary analysis. In addition, the programming needed to generate a subset of outputs will be validated by an independent validation vendor. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings.

All summary tables, listings, and figures (TLFs) will be presented by treatment groups as defined in Table 17.

Table 17 Treatment Display in TLFs

Treatment Group	Treatment Description in Data Display
1	Group 1 (GC Day 1 and 8)
2	Group 2 (GC + Trilaciclib Day 1 and 8)
3	Group 3 (GC + Trilaciclib Day 1/2 and 8/9)
Combined 2 and 3	Group 2 and Group 3

All statistical tests will be presented at a two-sided significance level of 95% unless otherwise specified. The primary comparison will be conducted between Group 3 (GC + Trilaciclib Day 1/2 and 8/9) and Group 1 (GC therapy alone). The two additional comparisons (i.e. GC + Trilaciclib Day 1 and 8 vs GC therapy only; Combined Trilaciclib + GC therapy vs GC therapy only) will be considered supportive of the primary analyses and will not be alpha protected. Where appropriate, model-based point estimates, together with their 95% CIs will be presented along with the two-sided p-values for the tests. P-value will be presented to 4 decimal places, if the p-value <0.0001, the value will be presented as "<0.0001".

For continuous data, the same number of decimal places as in the raw data will be presented when reporting mean, median, minimum and maximum; one more decimal place than in the raw data will be presented when reporting standard deviation and standard error (SE). The derived variables will be presented with 1 decimal place. Percentages will be reported with 1 decimal

point; if the count is 0, no percentage will be presented. Value of percentage less than 1% will be presented as "<1%." Value of percentage less than 100% but ≥ 99.5% will be presented as ">99%."

6.1.2. Handling of Missing Data

In general, the observed case (OC) data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing — no missing imputation will be performed. Safety analyses will be conducted on the OC data only. However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication. Please refer to Section 5.2.2 for the method of imputation of missing AE onset and stop date and Section 6.2.5 for the method of imputation of missing concomitant onset and stop dates.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Patients with missing data will be excluded only from analyses for which data are not available.

6.1.3. Visit Windowing

It is expected that there will be a variation between patients in the actual number of study days from the start of administration of study drug within each cycle – defined as Day 1 – to the dates that the scheduled visits occur. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 18. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patient listings.

For windowed visits during the treatment cycles, if more than 1 visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used. For the assigned follow-up visit, the last assessment in the window will be included in the summary.

Table 18 Visit Windowing

	Cycle 1/ Odd cycle (2X-1)				Cycle 2/ Even cycle (2X)				Post-treatment	Post-Treatment Visit + 60 days [e]
Visit	**C1D1**	**C1D8**	**C1D15**	**EOC1**	**C2D1**	**C2D8**	**C2D15**	**EOC2**		
Scheduled Day [a]	1	8	15	22	1	8	15	22		
Clinical Chemistry [b]	Day -3 to 1			2 to EOC	Day -3 to 1			2 to EOC	From first dose date of last cycle to first dose date of last cycle + 30	Relative to the first dose date of last cycle, the last assessment falling the window between 31 and 89.
Hematology [c] – cycles without skipped dose	Day -1 to 1	2 to 11	12 to 18	19 to EOC	Day -1 to 1	2 to 11	12 to 18	19 to EOC	From first dose date of last cycle to first dose date of last cycle + 30	Relative to the first dose date of last cycle, the last assessment falling the window between 31 and 89.
Hematology [c] – Cycles with skipped dose	Day -1 to 1	2 to 11	[d]	12 to EOC [d]	Day -1 to 1	2 to 11	[d]	12 to EOC [d]	From first dose date of last cycle to first dose date of last cycle + 30	Relative to the first dose date of last cycle, the last assessment falling the window between 31 and 89.

[a] The scheduled day is relative to the Day 1 of each cycle.
[b] Clinical chemistry may be obtained up to 72 hours prior to the first dose of each cycle.
[c] Hematology may be obtained up to 24 hours prior to dosing on Days 1 and 8 of each cycle, Day 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.
[d] For cycles where the Day 8/9 dose is skipped, there will not be a Day 15 visit, only End of Cycle
[e] 60 ± 7 days after the post-treatment visit only for hematologic parameters and CCI [redacted].
Note: Since (1) the end date of a cycle (EOC) is defined as the date of Day 1 study drug administration of the next cycle and (2) toxicity can alter the timing of Day 1, the actual day for EOC may vary. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as Day 22 relative to the first dose of the cycle with a +7 days visit window. Hence, for the last cycle, the window for EOC is 22-30.

6.1.4. Adjustment for Covariates

Prior to Protocol Amendment 3 Version 4.0, patient randomization was stratified by liver involvement (yes or no) and Eastern Cooperative Oncology Group (ECOG) status (0 or 1). With implementation of Amendment 3, the stratification factors were changed to number of prior lines of systemic therapy (0 vs. 1 or 2) and liver involvement. The number of prior lines of systemic therapy was retrospectively collected for those patients randomized prior to the Amendment 3. The efficacy analyses will use liver involvement and number of prior lines of therapy as covariates in statistical models. Where necessary, additional sensitivity analyses will be performed with liver involvement and ECOG status as covariates instead. Where not collected on the randomization page, values will be derived from other eCRF pages.

6.2. Analysis Methods

6.2.1. Patient Disposition

A summary table will be generated to provide the following by study part, as appropriate:

- Number of patients screened
- Number and percentage of screening failures
- Reason for screening failure
- Number of patients dosed
- Number of patients randomized
- Number of patients randomized and not dosed

A separate table will be presented to show the patients included in each analysis set and reason for exclusion from an analysis set.

Patient status at treatment and study completion will be listed and summarized. The listing will include whether patients discontinued from the treatment and the reasons for the discontinuation, along with the date of first and last dose and the date of completion or discontinuation from the treatment. The same information will be provided for patients who discontinued from the study. The following summaries will be added to the disposition table:

- End of treatment status (discontinued/ongoing for each study drug)
- Reason for study drug discontinuation (for each study drug)
- Number of patients going into Survival follow-up
- Number and percentage of patients who discontinued the study
- Reason for study discontinuation
- Death and reason for death

6.2.2. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics, such as age at informed consent date, age groups (18-65, >65-75, >75), gender, race, ethnicity, country, screening vital signs (body weight, height, BMI, BSA), ECOG status, prior lines of therapy, liver involvement, and smoking history (never smoker, former smoker and current smoker), will be summarized and listed.

6.2.3. Disease Characteristics

Disease characteristics including breast cancer gene (BRCA) classification, histological classification of initial breast cancer diagnosis, stage of initial breast cancer diagnosis, stage of TNBC diagnosis, stage at time of enrollment, and brain scan results will be summarized and listed. Date of initial breast cancer diagnosis, and date of TNBC diagnosis will be listed only.

6.2.4. Medical/Surgical History

Medical history will be coded to SOC and PT using MedDRA Version 20.1.

The number and percentage of randomized patients with any past medical/surgical history within each SOC and PT will be provided. A patient will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT). The conditions/diseases from medical history are those conditions/diseases that stopped prior to the study entry. Additionally, breast cancer surgeries will be summarized separately.

6.2.5. Concomitant Medications

All medication verbatim terms collected will be coded to Anatomical Therapeutic Classification (ATC) and PT using the WHO-DD Version Sep2017.

Prior medications are defined as those taken by the patient prior to the administration of study drug. Concomitant medications are defined as those taken by the patient at any time between the date of study drug administration and study completion/discontinuation. Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication did not occur during the treatment period.

Medications with onset/end dates that are partially/completely missing will be imputed as follows:

(i) For onset date:
- If only the day part of the medication onset date is missing and occurs in the same month and year as the first dose date of study drug, the date of first dose of study drug will be used as the onset date of the medication. Otherwise, the first day of the month will be used to complete the onset date of the medication;
- If the day and month parts of medication onset date are missing and occur in the same year as the first dose of study drug, the date of the first dose of study drug will be used as the onset date of the medication. Otherwise, January 1st will be used to complete the onset date of the medication;
- If the medication onset date is completely missing, the date of the first dose of study drug will be used as the onset date of the medication.

(ii) For end date:
- If only the day part of the medication end date is missing, the last day of the month will be used to complete the end date of the medication;
- If the day and month parts of the medication end date are missing, December 31st will be used to complete the onset date of the medication;
- If the medication end date is completely missing and the onset date of the medication occurs after the date of the first dose of study drug, the last date during the treatment period will be

used as the medication end date. Otherwise, the date of the first dose of study drug will be used as the medication end date.

Concomitant medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class.

All prior and concomitant medications will be presented in a patient listing.

6.2.6. Prior and Subsequent Anti-Cancer Therapy

The prior anti-cancer therapies, such as prior systemic anti-cancer therapy (Yes or No), prior breast cancer surgery (Yes or No), and prior radiotherapy (Yes or No), will be summarized and listed. All verbatim terms collected of prior and subsequent anti-cancer therapy will be coded to Anatomical Therapeutic Classification (ATC) and PT using the WHO-DD Version Sep2017.

The prior and subsequent anti-cancer therapy will be summarized separately by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class. The data will be presented in a patient listing.

For subsequent anti-cancer therapy, if the term contains the word “RADIATION” or ‘RADIOTHERAPY’, the therapy will be classified to radiotherapy; it is classified as systemic anti-cancer therapy unless the therapy can be grouped to surgery. The number and percentage of randomized patients receiving subsequent anti-cancer therapy will be provided by systemic anti-cancer therapy (by drug name and by line), radiotherapy, and surgery. All subsequent anti-cancer therapies will be presented in a patient listing.

6.2.7. Efficacy Analyses

All the efficacy variables will be summarized using descriptive statistics by cycle or visit, with the supportive data provided in patient listings. Data will be summarized using descriptive statistics and the between treatment comparison (trilaciclib days 1/2/8/9, trilaciclib days 1/8, and combined trilaciclib vs GC only), will be performed only for the primary and secondary endpoints outlined in Sections 5.1.1 – 5.1.3. The primary comparisons will be between trilaciclib days 1/2/8/9 vs. GC only and will be built into the multiplicity adjustment described in Section 6.2.7.1.3. Though relevant statistical tests will be conducted for other treatment comparisons, the information to be presented will be considered to be supportive. For these comparisons, all statistical tests will be conducted at a two-sided significance level of 5% unless otherwise specified. Where appropriate, model-based point estimates, together with their two-sided 95% CIs will be presented along with the two-sided p-value for the test unless otherwise specified. Graphical presentation of efficacy results will be performed as needed.

Unless otherwise specified, all analyses for the efficacy endpoints will be conducted for the treatment period which is defined to be between the date of randomization and the end of the last cycle.

6.2.7.1 Primary and Key Secondary Efficacy Analyses

6.2.7.1.1 Primary Efficacy Analyses

The primary efficacy endpoint, occurrence of SVN, is a binary response variable (Yes, No). It will be summarized using descriptive statistics by treatment group and will be analyzed to compare trilaciclib and GC only using modified Poisson regression (Zou, 2004) to account for the variable duration of the treatment period for each patient. The model will include baseline ANC as a covariate, the stratification factors of prior lines of systemic therapy (0 vs. 1 or 2) and liver involvement (Yes vs No), and treatment as a fixed effect. The logarithm transformation of number of cycles will be included as an offset variable in the modeling. The two-sided p-value, adjusted rate ratio (aRR) (trilaciclib vs GC only) and its 95% CIs will be presented.

For the other primary efficacy endpoint, DSN in Cycle 1 based on Strategy 1 in Section 5.1.1.2.1, a two-sided p-value will be calculated for the nonparametric analysis of covariance (ANCOVA) (Stokes 2012). The nonparametric ANCOVA will include study baseline ANC value as covariate, stratification factors of lines of systemic therapy (0 vs. 1 or 2) and liver involvement (Yes vs No), and treatment as a fixed effect. Along with the descriptive statistics, the mean difference and Hodges-Lehmann estimate of median difference between the two treatment groups, together with its 95% CIs will be provided. Additionally, DSN for each cycle will be presented using descriptive statistics.

6.2.7.1.2 Key Secondary Efficacy Analyses

Occurrence of RBC transfusions on/after 5 weeks on study is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1 except baseline HGB will be used as a covariate instead of baseline ANC in the modified Poisson model. Also, the offset will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles, and. An additional sensitivity analysis will look all transfusions during the treatment period, and all transfusions with a subset of subjects completing at least 1 cycle.

Occurrence of GCSF administration is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1.

Occurrence of platelet transfusion is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1 except baseline platelet count will be used as a covariate instead of baseline ANC in the modified Poisson model. Also, the offset will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles.

The total number of MAHE in Section 5.1.2.15.1.2.4 will be analyzed to compare trilaciclib and GC only using a negative binomial regression model to account for the potential over-dispersion. The model includes the stratification factors of prior lines of systemic therapy (0 vs. 1 or 2) and liver involvement (Yes vs No), and treatment as a fixed effect. The logarithm transformation of duration of treatment period divided by 7 (i.e. week) will be included as an offset variable in the modeling. The two -sided p-value, aRR (trilaciclib vs GC only) and its 95% CIs will be presented.

The total number of MAHE will be summarized descriptively, along with the weeks of duration, and the event rate per week (calculated as the total number of events/durations of treatment

period divided by 7 [i.e. week]). The cumulative incidence of events during the treatment period will be summarized and presented graphically in three-week intervals.

The total number of individual MAHE components (specified in Table 5) will be summarized similarly.

6.2.7.1.3 Multiplicity Adjustments

The clinical trial evaluates the objectives defined in terms of the comparison of Group 3 (GC + Trilaciclib Day 1/2 and 8/9) to Group 1 (GC therapy alone) on the primary and key secondary myelosuppression efficacy endpoints in Sections 5.1.1 and 5.1.2. The resulting multiplicity problem include the following 12 hypotheses of no effect:

- Hypothesis H_1. Comparison of Group 3 versus Group 1 for duration of severe (Grade 4) neutropenia in Cycle 1.
- Hypothesis H_2. Comparison of Group 3 versus Group 1 for occurrence of severe (Grade 4) neutropenia.
- Hypothesis H_3. Comparison of Group 3 versus Group 1 for occurrence of RBC transfusions on/after Week 5 on study.
- Hypothesis H_4. Comparison of Group 3 versus Group 1 for occurrence of G-CSF administration.
- Hypothesis H_5. Comparison of Group 3 versus Group 1 for occurrence of platelet transfusions.
- Hypothesis H_6. Comparison of Group 3 versus Group 1 for the MAHE composite.
- Hypothesis H_7. Comparison of Group 3 versus Group 1 for all-cause hospitalizations in the MAHE composite.
- Hypothesis H_8. Comparison of Group 3 versus Group 1 for all-cause dose reductions in the MAHE composite.
- Hypothesis H_9. Comparison of Group 3 versus Group 1 for febrile neutropenia in the MAHE composite.
- Hypothesis H_{10}. Comparison of Group 3 versus Group 1 for RBC transfusions on/after Week 5 in the MAHE composite.
- Hypothesis H_{11}. Comparison of Group 3 versus Group 1 for platelet transfusions in the MAHE composite.
- Hypothesis H_{12}. Comparison of Group 3 versus Group 1 for prolonged severe (Grade 4) neutropenia (> 5 days) in the MAHE composite.

A Hochberg-based gatekeeping procedure will be utilized to control the global familywise error rate across the multiple null hypotheses in the strong sense at a 1-sided α=0.025 level. The one-sided p-values for these comparisons will be used for the multiple test procedure, and the raw and adjusted 1-sided p-values will be provided in the summary.

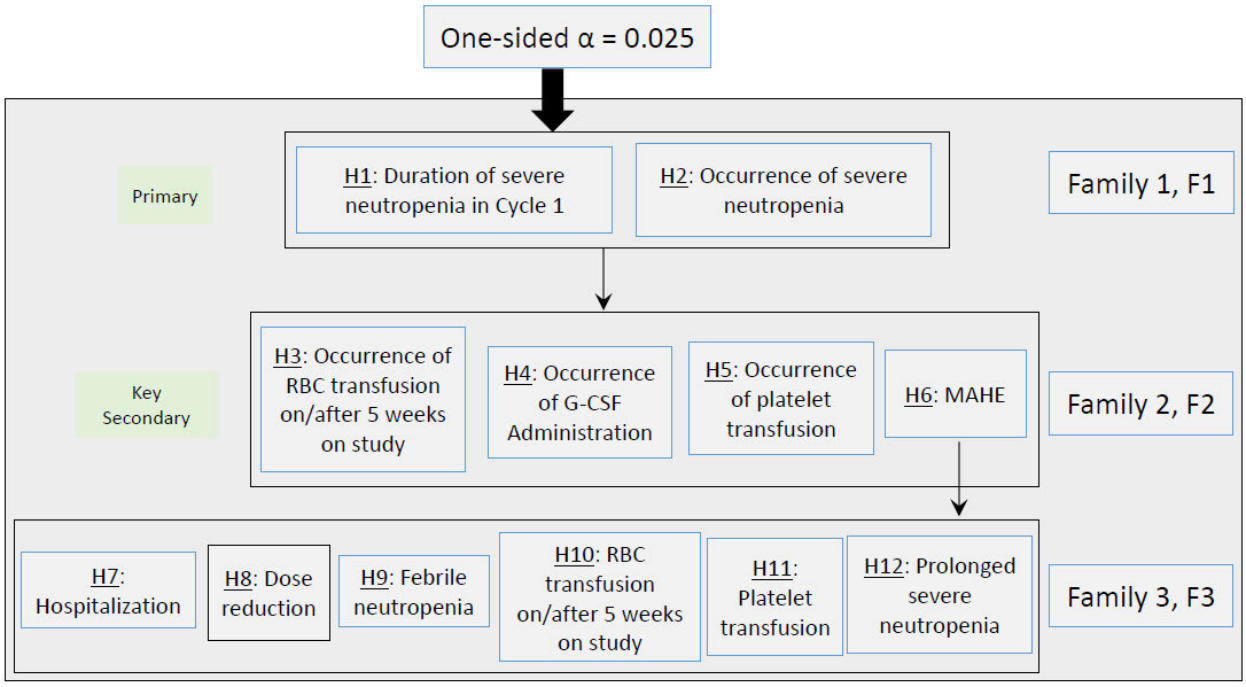
Gatekeeping procedure with logical restrictions

A Hochberg-based gatekeeping procedure satisfies the positive dependence condition given the 1-sided setting. The procedure is built using the mixture methodology developed in Dmitrienko and Tamhane (2011) and accounts for the logical restrictions among the 12 hypotheses displayed in

Figure **1** by performing multiplicity adjustments in three steps. The logical restrictions can be achieved by defining the parallel set and serial set for each individual hypothesis based the tree-structured procedure introduced by Dmitrienko et al (2007).

- Step 1. The Group 3 versus Group 1 comparisons for Family 1 (hypotheses H_1 and H_2) are performed using a truncated version of the Hochberg procedure. The truncation parameter γ is set to 0.5.
- Step 2. The Group 3 versus Group 1 comparisons for Family 2 (hypotheses H_3, H_4, H_5, and H_6) are performed using a truncated version of the Hochberg procedure if there is at least one significance in Step 1. Specifically, the hypotheses H_3, H_4, H_5, and H_6 depend on the hypotheses H_1 and H_2, ie, H_3, H_4, H_5, and H_6 are tested only if at least one of the hypotheses H_1 and H_2 is rejected. The truncation parameter γ is set to 0.5.
- Step 3. The Group 3 versus Group 1 comparisons for Family 3 (hypotheses H_7, H_8, H_9, H_{10}, H_{11}, and H_{12}) are performed using the regular Hochberg test if H_6 is significant in Step 2.

Figure 1 Graphical Display of the Hochberg-based Gatekeeping Procedure



The regular Hochberg test is defined in Dmitrienko et al. (2009) and the truncated Hochberg test is defined in Dmitrienko, Tamhane and Wiens (2008). The decision rules used in the regular and truncated Hochberg tests will be detailed in the following. In general terms, the truncated version of the Hochberg test is defined as a convex combination of the regular Hochberg and Bonferroni tests. An important parameter of the truncated Hochberg test is the truncation parameter γ which

ranges between 0 and 1. If the truncation parameter γ is set to 0, the truncated Hochberg test simplifies to the Bonferroni test. On the other hand, if the truncation parameter γ is set to 1, the truncated Hochberg test is identical to the regular Hochberg test. The truncated Hochberg test satisfies the separability condition (Dmitrienko, Tamhane and Wiens, 2008) if the truncation parameter γ is strictly less than 1. This condition ensures that in each step of the testing algorithm the error rate can be transferred to the next step provided at least one Group 3 versus Group 1 comparison is significant in the current step without inflating the overall type I error rate (Huque, 2016; FDA, 2017).

Testing algorithm

This section describes the implementation of the Hochberg-based gatekeeping procedure. The testing algorithm relies on the general approach to defining multistage gatekeeping procedures based on mixtures of multiple tests proposed in Dmitrienko and Tamhane (2011).

Decision rules

The aforementioned 12 hypotheses are grouped into 3 families:

- Family 1 (F_1) includes the hypotheses H_1 and H_2.
- Family 2 (F_2) includes the hypothesis H_3, H_4, H_5, and H_6.
- Family 3 (F_3) includes the hypotheses H_7, H_8, H_9, H_{10}, H_{11}, and H_{12}.

Using more compact notation, the families are defined as follows:

$$F_1 = \{H_i, i \in N_1\},\ F_2 = \{H_i, i \in N_2\},\ F_3 = \{H_i, i \in N_3\}.$$

where the index sets are defined as $N_1 = \{1, 2\},\ N_2 = \{3, 4, 5, 6\}, N_3 = \{7, 8, 9, 10, 11\ 12\}$. Let t_i and p_i denote the test statistic and 1-sided p-values associated with the hypotheses, respectively. Let α denote the global familywise error rate, i.e., one-sided $\alpha = 0.025$.

Consider the closed family associated with Families 1, 2 and 3, i.e., a family of all non-empty intersections of the twelve hypotheses. Each intersection will be identified by an index set

$$I \subseteq N\ = \{1, \ldots, 12\}$$

(note that the empty set is excluded). For example, the index vector $I = \{1, 2, 5, 8\}$ corresponds to the intersection of the hypotheses H_1, H_2, H_5, and H_8.

To construct the Hochberg-based gatekeeping procedure that controls the global familywise error rate in the strong sense at an α level, an α-level test needs to be defined for each intersection in the closed family. The multiple test and associated p-value for an intersection are computed in two steps.

Step 1: Define p-values for subset intersections

Consider an intersection corresponding to the index set $I \subseteq N$ and define the index sets $I_k = I \cap N_k$, $k = 1, 2, 3$. The p-values for the index sets I_1, I_2, and I_3 are computed as follows:

Let n_1 denote the number of hypotheses included in I_1 and let $m_1 = n_1$. If $n_1 > 0$, the truncated Hochbergp-value is defined using the ordered p-values associated with the hypotheses included in the index set I_1, denoted by

$$p_{1(1)} \leq \cdots \leq p_{1(m_1)}$$

The truncated Hochberg p-value for the index set I_1 is given by

$$p(I_1) = \min_{i=1,\cdots,m_1} \frac{p_{1(i)}}{\frac{\gamma_1}{m_1 - i + 1} + \frac{1-\gamma_1}{2}}$$

Here γ_1 is the pre-specified truncation parameter in Family 1. Choosing a larger value of γ_1 improves the power of comparisons in Family 1, and γ_1 is set to 0.5.

Further, let n_2 denote the number of hypotheses included in the index set I_2. If $n_2 > 0$, consider the hypotheses in the index set I_2 and remove the hypotheses that are not consistent with the logical restrictions defined in
Figure **1**. Let m_2 denote the number of hypotheses remaining in the index set I_2 after this logical restriction operation. If $m_2 > 0$, let

$$p_{2(1)} \leq \cdots \leq p_{2(m_2)}$$

denote the ordered p-values for the hypotheses remaining in the index set I_2. The truncated Hochberg p-value for I_2 is given by

$$p(I_2) = \min_{i=1,\cdots,m_2} \frac{p_{2(i)}}{\frac{\gamma_2}{m_2 - i + 1} + \frac{1-\gamma_2}{4}}$$

where γ_2 is the pre-specified truncation parameter in Family 2, which plays the same role as γ_1 in Family 1, and γ_2 is set to 0.5.

Finally, let n_3 denote the number of hypotheses included in I_3. If $n_3 > 0$, remove the hypotheses that are not consistent with the logical restrictions defined in
Figure **1**. Let m_3 denote the number of hypotheses remaining in the index set I_3 after this logical restriction operation. If $m_3 > 0$, let

$$p_{3(1)} \leq \cdots \leq p_{3(m_3)}$$

denote the ordered p-values for the hypotheses remaining in the index set I_3. The Hochberg p-value for I_3 is given by

$$p(I_3) = \min_{i=1,\cdots,m_3} \frac{p_{3(i)}}{\frac{1}{m_3 - i + 1}}$$

Step 2: Define overall p-value

The overall p-value for the intersection corresponding to the index set I is computed by combining the p-values associated with the index sets I_1, I_2, and I_3. Consider the following three scenarios:

- If $n_1 > 0$, the overall p-value is found using the following mixing function:

$$p(I) = \min\left(\frac{p(I_1)}{b_1}, \frac{p(I_2)}{b_2}, \frac{p(I_3)}{b_3}\right)$$

where $b_1 = 1,\ b_2 = b_1(1 - f_1),\ b_3 = b_2(1 - f_2)$ and f_1 and f_2 are computed based on the error rate functions of the truncated Hochberg tests used in Families 1 and 2. These quantities are defined below.

- If $n_1 = 0$ and $n_2 > 0$, the overall p-value is given by

$$p(I) = \min\left(\frac{p(I_2)}{b_2}, \frac{p(I_3)}{b_3}\right)$$

where $b_2 = 1,\ b_3 = b_2(1 - f_2)$.

- If $n_1 = 0, n_2 = 0$ and $n_3 > 0$, the overall p-value is given by

$$p(I) = \frac{p(I_3)}{b_3}$$

where $b_3 = 1$.

The error rate function of the truncated Hochberg test with the truncation parameter γ_k for testing an intersection corresponding to the index set I_k, $k = 1, 2$, is defined as

$$e_k(I_k) = P[p(I_k) \leq \alpha]$$

and $f_k = e_k(I_k)/\alpha$, $k = 1, 2$. It is shown in Brechenmacher et al. (2011) that

$$e_k(I_k) = [\gamma_k + (1 - \gamma_k)|I_k|/n_k]\alpha$$

if the index set I_k is non-empty and $e_k(I_k) = 0$ the index set I_k is empty. Here $|I_k|$ denotes the number of hypotheses included in the index set I_k.

As shown in Dmitrienko and Tamhane (2011), the resulting test for the intersection corresponding to the index set I is an α-level test. This implies that the Hochberg-based gatekeeping procedure controls the global familywise error rate in the strong sense at a one-sided $\alpha = 0.025$.

Multiplicity-adjusted p-values

Multiplicity-adjusted p-values for the Hochberg-based gatekeeping procedure are computed using the closure principle. For each hypothesis, the adjusted p-value is defined as the maximum over the p-values associated with the intersections in the closed family that include the hypothesis of interest. For example, the adjusted p-value for H_2 is the maximum over the p-values for intersections containing H_2. The calculations are performed using the decision matrix algorithm, see Dmitrienko and Tamhane (2011).

Regular and truncated Hochberg tests

Consider a general problem of testing m null hypotheses denoted by $H_1, \ldots, H_m$. Let $p_1, \ldots, p_m$ denote the associated raw p-values. Further, let $p_{(1)} < \cdots < p_{(m)}$ denote the ordered p-values and $H_{(1)} < \cdots < H_{(m)}$ denote the hypotheses corresponding to the ordered p-values.

The regular Hochberg test is based on the following testing algorithm:

- Step 1: If $p_{(m)} > \alpha$, accept $H_{(m)}$ and go to Step 2, otherwise reject all null hypotheses and stop.

- Step $i = 2, \ldots, m-1$: If $p_{(m-i+1)} > \alpha/i$, accept $H_{(m-i+1)}$ and go to Step $i+1$, otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$, otherwise reject $H_{(1)}$.

The truncated Hochberg test with the truncation parameter γ is based on the following testing algorithm:

- Step 1: If $p_{(m)} > [\gamma + (1-\gamma)/m]\alpha$, accept $H_{(m)}$ and go to Step 2, otherwise reject all null hypotheses and stop.
- Step $i = 2, \ldots, m-1$: If $p_{(m-i+1)} > [\gamma/i + (1-\gamma)/m]\alpha$, accept $H_{(m-i+1)}$ and go to Step $i+1$, otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$, otherwise reject $H_{(1)}$

6.2.7.1.4 Robustness of Primary and Key Secondary Efficacy Analyses

A binary response variable (Yes, No) will be analyzed to compare trilaciclib and GC only using stratum-adjusted method to account for the liver involvement (Yes or No) and number of prior lines of therapy (0, 1-2) as the stratification factor. The adjusted proportion difference (trilaciclib vs GC only) and its 95% CIs will be calculated using Cochran-Mantel-Haenszel (CMH) weight outlined in Kim et al. 2013. The two-sided p-value will be calculated using stratified exact CMH method. Additionally, three sets of sensitivity analysis will be conducted to evaluate the robustness of the results from primary or key secondary analyses for a binary response variable (Yes, No).

(i) For patients who die during the treatment period without experiencing an event, Yes will be assigned to the variable.

(ii) After the imputation from (i), a worst-comparison analysis will be done to establish a stringent boundary of the treatment effect. Patients who die during the treatment period will still be set to Yes, and patients who discontinue the study prior to the July 30, 2018 data cutoff date without experiencing an event will then be imputed. If the patient is from the GC only group, No will be assigned to the variables, Yes will be assigned to the trilaciclib groups.

(iii) After the imputation from (i), a tipping-point analysis (Yan et al,. 2009) will be performed by assigning the response to the variable for patients who discontinue the study early during the treatment period without experiencing an event.

The tipping-point analysis assumes all possible combinations of numbers of Yes and No for the missing responses (defined as patients without an event who have discontinued the study prior to the July 30, 2018 data cutoff date) in the trilaciclib and GC only groups. For example, let n_t be the number of randomized trilaciclib patients with missing response and n_c be the number of randomized GC only patients with missing responses. For the trilaciclib patients with missing values, there are $n_t + 1$ possible assumptions for number of No (i.e. 0, 1, 2, …, to n_t); for the GC only patients with missing values, there are $n_c + 1$ possible assumptions for number of No. Therefore, there are total of $(n_t + 1) \times (n_c + 1)$ possible combination of assumptions for number of No and Yes for the trilaciclib and GC only patients with missing responses. The un-stratified exact CMH method will be

performed on the available responses with each of these $(n_t + 1) \times (n_c + 1)$ assumptions and will be summarized. A figure will be presented with points representing each possible combination where the significant p-value 'tips' to greater than a one-sided 0.025, which would represent a change in the study conclusions. Clinical justification will be provided to evaluate whether the assumption is plausible.

Each of the analyses will be repeated using two additional distinct data sets to evaluate the confounding effect of GCSF administration: inclusion of only those patients or cycles who had concurrent GCSF administration; and inclusion of only those patients or cycles who did NOT have concurrent GCSF administration. The "with" and "without" GCSF analyses are subsets of the total number of patients or cycles.

Each of the analyses will be similarly repeated for subsets of cycles with and without skipped doses.

Time-to-event endpoints will be summarized using Kaplan-Meier method, and the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs will be calculated for

- DSN, Strategy 2 (refer to Section 5.1.1.2.2). Additionally, DSN for each cycle will be presented using descriptive statistics.
- Time-to-first MAHE endpoints (overall and individually) in Section 5.1.2.4.

In addition to the summary from Kaplan-Meier method, the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the stratification factors. The hazard ratio (HR) between the two treatments (trilaciclib vs GC only), together with its 95% CIs will be calculated from a Cox proportional hazard model in which treatment and the stratification factors will be included as fixed effects.

For the time (days) to first occurrence of a MAHE event, a graphical display of cumulative incidence will be presented.

The primary and key secondary efficacy endpoints are based on the ITT analysis set, and the analysis will be repeated for the mITT analysis set and PP analysis set.

6.2.7.2 Supportive Secondary Efficacy Analyses

6.2.7.2.1 Analyses of Objective Response

The patients in each category of TPR according to the investigator tumor assessment (CR, PR, SD, PD, or NE) will be presented in a data listing. The number and percentage of patients in each category of BOR (Confirmed CR, Confirmed PR, SD, PD, or NE), ORR, $ORR_{UNCONFIRMED}$ and CBR according to the investigator tumor assessment (Confirmed CR, Confirmed PR, SD, PD, or NE) will be summarized. Detailed information of deriving tumor relevant responses is provided in Section 5.1.3.1.4.

Similar analyses will be repeated based on the derived responses according to the RECIST Version 1.1.

Estimates of response rate, along with its associated exact 95% two-sided CIs using Clopper-Pearson method will be computed for ORR and CBR within each treatment group.

The binary endpoint (Yes, No) of ORR for the two treatments (trilaciclib and GC only) will be analyzed to compare trilaciclib and GC only using stratum-adjusted method to account for the stratification factors. The adjusted proportion difference (trilaciclib vs GC only) and its 95% CIs will be calculated using CMH weight outlined in Kim et al. 2013. The two-sided p-value will be calculated using stratified exact CMH method.

The analyses are based on the response evaluable analysis set. The supportive data listings will also be provided.

6.2.7.2.2 Analyses of DOR, PFS, and OS

DOR (investigator and derived) will be summarized using Kaplan-Meier method, and the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs will be calculated. It will be based on the response evaluable analysis set. The supportive data listings will also be provided.

PFS (derived, and derived with clinical progression) and OS will be similarly summarized, and in addition to the quartile summary from Kaplan-Meier method, Kaplan-Meier estimates will be provided for the survival rates at 3, 6, 9, and 12 months along with their 95% CIs. Comparison will also be conducted between trilaciclib and GC only. The two-sided p-value from a Cox proportional hazard model will be presented, the model includes treatment and stratification factors as fixed effects. The HR between the two treatment groups, together with its 95% CIs will be presented.

Both PFS and OS will be based on the ITT analysis set. For the PFS, the derived endpoint based on only radiologic progression will be considered as the primary, and the derived endpoint based on both radiologic and clinical progression will be considered as supportive.

6.2.7.2.3 Analyses of Hematology Lab Values

For the endpoints specified in Section 5.1.3.3 and 5.1.3.4, in addition to descriptive statistics summary, graphical displays will be provided to facilitate evaluation of trends in the change in a given variable over time. Moreover, each of the ANC change over time analysis (i.e. observed value at windowed visit and cycle nadir) specified above will be done using three distinct data sets to evaluate the confounding effect of GCSF administration: all patients or cycles regardless of GCSF administration; inclusion of only those patients or cycles who had concurrent GCSF administration; and inclusion of only those patients or cycles who did NOT have concurrent GCSF administration. The “with” and “without” GCSF analyses are subsets of the total number of patients or cycles.

6.2.7.2.4 Analyses of Other Binary Efficacy Endpoints

The following binary response variables (Yes, No) will be analyzed using the same method for occurrence of SVN except baseline ANC will not be a covariate in the modified Poisson model. See Section 6.2.7.1.1:

- Occurrence of a Grade 3 or 4 hematologic toxicity during the treatment period (refer to Section 5.1.3.2);
- Occurrence of an ESA administration during the treatment period (refer to Section 5.1.3.5);

- Occurrence of an IV antibiotic administration during the treatment period (refer to Section 5.1.3.6); The offset in the modified Poisson model will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles. Additionally, total number of IV antibiotic administrations will be summarized descriptively.
- Occurrence of an infection SAE during the treatment period (refer to Section 5.1.3.7); The offset in the modified Poisson model will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles. Additionally total number of infection SAEs will be summarized descriptively.
- Occurrence of all-cause dose reductions during the treatment period (refer to Section 5.1.2.4.2);
- Occurrence of a Grade 4 and Grade 3 or 4 thrombocytopenia during the treatment period (refer to Section 5.1.3.9);

CCI

[redacted]

6.2.8. Safety Analyses

All safety analyses will be based on the safety analysis set, as defined in Section 3.1.3. Descriptive statistics will be used to summarize the safety outcomes. The continuous safety variables will be summarized at each visit including end of each cycle (the last non-missing assessment during the cycle), end of treatment (the last non-missing assessment during the treatment period), and end of study (the last non-missing assessment during the whole study), if applicable. No inferential analyses of safety data are planned unless otherwise specified.

6.2.8.1. Chemotherapy Exposure and Compliance Analyses

Duration on treatment and number of cycles will be summarized by treatment. For each study drug, the dosing endpoints described in Section 5.2.1 will be summarized by treatment.

Dose modifications will be summarized for each study drug (gemcitabine, carboplatin or trilaciclib) including the following:

- Number of cycles received;
- Number of skipped doses;
- Number of dose reductions;
- Number of dose interruptions;
- Number of patients with skipped doses;
- Number of patients with dose reductions;
- Number of patients with dose interruptions.

The number of cycles delayed, the number and percentage of patients experiencing a treatment cycle delay, and reason for cycle delay will be summarized by treatment. The study dosing records and the derived dosing endpoints will be listed.

6.2.8.2. Adverse Events

Number and incidence rates of AEs will be summarized by SOC and/or PT for the following categories of TEAEs: all AEs, SAEs, AEs leading to death, and AEs leading to study drug discontinuation or study withdrawal. Patients with more than one occurrence of the same SOC (PT) will be counted only once within the SOC (PT) categorization.

AEs will also be summarized similarly by CTCAE grade and relationship to any study drug (gemcitabine, carboplatin or trilaciclib), and by relationship to each drug. Should a patient experience more than one occurrence of the same SOC (PT), the patient's worst occurrence (worst grade/most related causality) will be retained in the tabulation.

All AEs, including AEs that started prior to the study medication, will be presented in patient listings. In addition, separate listings of all SAEs, AEs leading to death, drug-related AEs, and AEs leading to study drug discontinuation or study withdrawal will be provided.

The criteria for identifying infusion related reaction AEs or hematologic toxicity AEs are described in Section 5.2.2. A summary table showing the incidence of each category of AEs related to infusion and related to hematologic toxicity will be presented along with its supportive data listing.

6.2.8.3. Laboratory Evaluations

For hematology and clinical chemistry labs, the observed values and change from baseline will be summarized separately for cycles with and without a skipped dose for each visit during the treatment period using descriptive statistics.

Toxicities for clinical labs will be characterized according to CTCAE, Version 4.03 (Table A-1 of Appendix when possible), and the frequency and percentage of patients with each CTCAE grade for each visit (separately by cycles with and without a skipped dose) during the treatment period will be described. Moreover, any occurrence of grade 3 or grade 4 during the treatment period will be summarized, and shift in grade from baseline to the worst post-baseline value will be summarized. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

Listings of all laboratory data with a flag for cycles with a skipped dose, normal reference ranges, and CTCAE grades (when possible) will be provided.

6.2.8.4. Vital Signs

For vital sign parameters (Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Temperature, and Weight) the observed values and change from baseline will be summarized using descriptive statistics at each visit during the treatment period.

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (defined in Table 14) during the treatment period will be presented. A listing of all vital sign data will be provided.

6.2.8.5. Performance Status

Descriptive statistics will be presented for ECOG score for the observed values and change from baseline. A listing of ECOG score for all patients will be provided.

6.2.8.6. Physical Examination

A listing of screening physical examination findings for all patients will be provided (where available).

6.2.8.7. ECG

Descriptive statistics will be presented for each ECG parameter for the observed values and change from baseline to post baseline. A listing of all ECG data will be provided.

The criteria for potentially clinically significant findings are defined in Table 16. The frequency and percentage of patients with any potentially clinically significant findings during the treatment period will be presented. The supportive data will be provided in patient data listings.

6.2.9. Subgroup Analyses

The PFS, OS, and MAHE will be examined in the following subgroups:

- Age group (ages <65; >65).
- Liver involvement (Yes; No).
- ECOG performance status (0; 1).
- Prior lines of therapy (0; 1-2).
- Race (Caucasian; non-Caucasian).
- Region (US; Ex-US).
- BRCA classification (Positive; Unknown)
- Histological classification (TNBC; Acquired TNBC)

Descriptive statistics by treatment group will be presented for each subgroup of patients. Additional subgroups or endpoints may be identified and explored.

6.2.10. Pharmacokinetic Analysis

The PK analysis for a subset of patients will be documented separately and is not covered in this SAP.

CCI

[redacted]

6.2.12. Planned Analysis

The final myelosuppression analysis will be conducted after all patients have had the opportunity to receive at least 12 weeks of treatment. All study data collected through the time of the final myelosuppression analysis data cut will be included. This includes, but is not limited to the final myelosuppression analysis, interim ORR analysis based on investigator assessment, and interim PFS/OS analysis.

The time of analysis with at least 80% of patients having experienced a progression will be considered to be final PFS analysis. Patients will be followed for survival until at least 70% of the patients have died, and a final OS analysis will be done then. CCI [redacted]. Reported results, with the exception of the myelosuppression analyses, will be cumulative in nature, including all data collected during the entire study; the myelosuppression analyses will be complete at the final analysis and no additional data will be expected.

7. CHANGE FROM THE PROTOCOL

The timing of the final analysis, analysis sets, and endpoints were updated based on scientific advice, regulatory guidance, and feedback on other trilaciclib studies. The endpoints and analyses listed below are based on the Statistics Section in the Protocol Amendment 3, dated 31 August 2017. The list displays the endpoints and analyses which are removed from the initial analysis and are therefore not described in the SAP.

Protocol Section 13.3.1 (Efficacy Endpoints):

- Hematologic kinetic endpoints:
    - Change and percent change in hematologic parameter values from predose for a particular cycle to the end of that cycle
    - Change and percent change in hematologic parameter values from predose for a particular cycle to nadir for that cycle
    - Rate of change in hematologic parameter values from predose for a particular cycle to nadir for that cycle
    - Change and percent change in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Rate of change in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Area under the curve in hematologic parameter values from predose for a particular cycle to the end of that cycle
    - Area under the curve in hematologic parameters from predose for a particular cycle to nadir for that cycle
    - Area under the curve in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Time to hematologic parameter value nadir by cycle
    - Time to return to predose hematologic parameter values by cycle
    - Proportion of patients with a return to predose hematologic parameter values by cycle
- Hematologic toxicity endpoints:
    - Proportion of patients with a hematologic toxicity recovery by cycle.
    - Time to hematologic toxicity recovery by cycle

Protocol Section 13.3.2.1 (Analysis of Hematologic Parameter Kinetic Endpoints)

- Additional tabulations for each cycle of treatment in maximum postnadir values.

- The tabulation of the changes and percent changes from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle values for each cycle of treatment.
- Analysis of covariance (ANOVA) models on hematologic parameter kinetic endpoints
- Summarization of time to nadir.
- Descriptive statistics and ANOVA of AUC in hematologic parameters
- Repeated-measures model of AUC
- Summary of proportion of patients return to predose value for each cycle, calculation on incidence rate, adjusting for cumulative exposure
- Analysis of time to return to predose level for each cycle using Kaplan-Meier method.
- Analysis of Time to return to postnadir predose levels

Protocol Section 13.3.2.2 (Analysis of Hematologic Toxicity Endpoints)

- Calculation and analysis of incidence rate of hematologic toxicity, adjusting for cumulative exposure
- Calculation and analysis of toxicity rate relative to cumulative exposure (total number of toxicities divided by cumulative exposure).
- Recurrent events model estimating the incidence of Grade 3 or higher hematologic toxicities and testing for the difference between treatment groups.
- For each hematologic parameter and cycle, the shift summaries of the following:
    - From predose toxicity to maximum on treatment toxicity;
    - from predose toxicity to end of cycle toxicity;
    - from maximum postdose toxicity to end of cycle toxicity.

Protocol Section 13.3.2.4 (Other Efficacy Endpoints)

- The number and percent of infections summarized by maximum severity
- The infection rate: The number of infections occurring during the Treatment divided by cumulative exposure.

CCI [redacted]

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Table A-1 Clinical Laboratory Parameters CTCAE Criteria

Parameter	Grade				
	1	2	3	4	5
Albumin	<LLN – 3 g/dL; <LLN – 30 g/L	<3 – 2 g/dL; <30 – 20 g/L	<2 g/dL; <20 g/L	-	-
ALP	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
ALT	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
AST	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	-
Calcium (Hypercalcemia)	Corrected serum calcium of >ULN – 11.5 mg/dL; >ULN – 2.9 mmol/L	Corrected serum calcium of >11.5 – 12.5 mg/dL; >2.9 – 3.1 mmol/L	Corrected serum calcium of >12.5 – 13.5 mg/dL; >3.1 – 3.4 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L	-
Calcium (Hypocalcemia)	Corrected serum calcium of <LLN – 8.0 mg/dL; <LLN – 2.0 mmol/L	Corrected serum calcium of <8.0 – 7.0 mg/dL; <2.0 – 1.75 mmol/L	Corrected serum calcium of <7.0 – 6.0 mg/dL; <1.75 – 1.5 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L	-
CK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	-
Creatinine	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN	>6.0 x ULN	-
GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Glucose (Hyperglycemia)	Fasting glucose value >ULN – 160 mg/dL; Fasting glucose value >ULN – 8.9 mmol/L	Fasting glucose value >160 – 250 mg/dL; Fasting glucose value >8.9 – 13.9 mmol/L	Fasting glucose value >250 – 500 mg/dL; Fasting glucose value >13.9 – 27.8 mmol/L	Fasting glucose value >500 mg/dL; Fasting glucose value >27.8 mmol/L	-
Glucose (Hypoglycemia)	<LLN – 55 mg/dL; <LLN – 3.0 mmol/L	<55 – 40 mg/dL; <3.0 – 2.2 mmol/L	<40 – 30 mg/dL; <2.2 – 1.7 mmol/L mmol/L	<30 mg/dL; <1.7 mmol/L	-
Hemoglobin	<LLN – 10.0 g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L	<10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-	-
Potassium (Hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	-

Table A-1 Clinical Laboratory Parameters CTCAE Criteria

Parameter	Grade				
	1	2	3	4	5
Potassium (Hypokalemia)	<LLN – 3.0 mmol/L	-	<3.0 – 2.5 mmol/L	<2.5 mmol/L	-
Lymphocyte	<LLN – 800/mm3; <LLN – 0.8 x 10e9 /L	<800 – 500/mm3; <0.8 – 0.5 x 10e9 /L	<500 – 200/mm3; <0.5 – 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
ANC	<LLN – 1500/mm3; <LLN – 1.5 x 10e9 /L	<1500 – 1000/mm3; <1.5 – 1.0 x 10e9 /L	<1000 – 500/mm3; <1.0 – 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Phosphates	<LLN – 2.5 mg/dL; <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL; <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL; 0.6 – 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L	-
Platelet Count	<LLN – 75,000/mm3; <LLN – 75.0 x 10e9 /L	<75,000 – 50,000/mm3; <75.0 – 50.0 x 10e9 /L	<50,000 – 25,000/mm3; <50.0 – 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Sodium (Hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	-
Sodium (Hyponatremia)	<LLN – 130 mmol/L	-	<130 – 120 mmol/L	<120 mmol/L	-
Urate	>ULN – 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN – 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L	-
White blood cell	<LLN – 3000/mm3; <LLN – 3.0 x 10e9 /L	<3000 – 2000/mm3; <3.0 – 2.0 x 10e9 /L	<2000 – 1000/mm3; <2.0 – 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-

LLN=lower limit of normal range; ULN=upper limit of normal range.

STATISTICAL ANALYSIS PLAN
– Region 2 –

Study Title:	Phase 2 Study of the Safety, Efficacy, and Pharmacokinetics of G1T28 in Patients with Metastatic Triple Negative Breast Cancer Receiving Gemcitabine and Carboplatin Chemotherapy
Sponsor	G1 Therapeutics 79 T.W. Alexander Drive 4501 Research Commons, Suite 100 Research Triangle Park, NC 27709
Name of Test Drug:	G1T28
Protocol Number:	G1T28-04
Phase:	Phase 2
Analysis Plan Version	Version 1.0
Version Date	28 September 2018

APPROVAL SIGNATURES

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aRR	Adjusted Rate Ratio
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under Curve
β-HCG	Beta Human Chorionic Gonadotropin
BMI	Body Mass Index
BOR	Best Overall Response
BPM	Beats Per Minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CDK	Cyclin Dependent Kinase
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOI	End of Infusion
ESA	Erythropoietin Stimulating Agent
CCI [redacted]	[redacted]
G1T28	Trilaciclib
GC	Gemcitabine and Carboplatin
GCSF	Granulocyte Colony-Stimulating Factor
HR	Hazard Ratio
ICH	International Conference on Harmonization
ITT	Intent-to-treat

Abbreviation	Term
IV	Intravenous
LD	Longest Diameter
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal Range
MAHE	Major Adverse Hematologic Event
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
Nadir	The Lowest Point
NE	Not Evaluable
CCI	[redacted]
NTL	Non-Target Lesion
OC	Observed Case
ORR	Objective Response Rate
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
CCI	[redacted]
PP	Per Protocol
PR	Partial Response
CCI	[redacted]
PT	Preferred Term
CCI	[redacted]
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
CCI	[redacted]
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease
SOC	System Organ Class
SVN	Severe Neutropenia
TEAE	Treatment Emergent AE
TL	Target Lesion
TLFs	Tables, Listings, and Figures
TNBC	Triple Negative Breast Cancer
TPR	Time Point Response
ULN	Upper Limit of Normal Range
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the analyses to be performed following the completion of Study G1T28-04, Phase 2 Study of the Safety, Efficacy, and Pharmacokinetics of G1T28 in Patients with Metastatic Triple Negative Breast Cancer Receiving Gemcitabine and Carboplatin Chemotherapy. The SAP is based on the G1T28-04 Protocol Version 4, dated 31 August 2017.

Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the database. Any deviations from these guidelines will be documented in the clinical study report (CSR).

The myelosuppression efficacy endpoints and statistical analysis methods described in this SAP are reflective of scientific advice obtained in both the US and EU for evaluation of trilaciclib for the reduction of chemotherapy-induced myelosuppression. While the primary objective of G1T28-04 does not explicitly state that the trial has been designed to evaluate the effects of trilaciclib on chemotherapy-induced myelosuppression, the endpoints of AEs and laboratory values used to evaluate safety and tolerability are the same endpoints used to evaluate effects on chemotherapy-induced myelosuppression. The data collection for this trial was appropriate for the analysis of these myelosuppression endpoints, and the defined endpoints in this SAP are consistent with the overall strategy/rationale for Study G1T28-04.

2. STUDY DETAILS

2.1. Study Objectives

The primary, secondary, and CCI objectives of this study as defined in the study protocol are presented in Table 1.

Table 1 G1T28-04: Study Objectives

Primary Objective[a]
Assess the safety and tolerability of trilaciclib administered with GC therapy
Secondary Objectives[a]
Assess tumor response and duration of response based on RECIST, Version 1.1
Assess PFS and OS
Assess dose intensity of gemcitabine and carboplatin
Assess the PK profile of trilaciclib
Assess the PK profile of gemcitabine and carboplatin when administered with and without trilaciclib
Assess the hematologic profile (kinetics and incidence/duration/frequency of toxicities) of trilaciclib administered with GC therapy
Assess the incidence of febrile neutropenia
Assess the incidence of infections
Assess the utilization of RBC and platelet transfusions
Assess the utilization of hematopoietic growth factors
Assess the utilization of systemic antibiotics
Assess the incidence of chemotherapy dose reductions and dose interruptions overall
Assess the incidence of Grade 2 or greater nephrotoxicity
Determine the dose schedule of trilaciclib administered with GC therapy
CCI

GC therapy = gemcitabine + carboplatin on Days 1 and 8 or Days 2 and 9 of 21-day cycles; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; CCI ; RBC = red blood cell; CCI ; RECIST = Response Evaluation Criteria in Solid Tumors

a. The objectives will be assessed for both schedules of trilaciclib (Days 1 and 8 or Days 1, 2, 8, and 9 in 21-day cycles) administered prior to GC therapy (Days 1 and 8 or Days 2 and 9 in 21-day cycles, respectively)

2.2. Study Design

This is a multicenter, randomized, open-label, Phase 2 study of the safety, efficacy, and pharmacokinetics (PK) of trilaciclib in combination with gemcitabine and carboplatin (GC) therapy for patients with metastatic triple negative breast cancer (TNBC). A total of approximately 90 patients will be randomly assigned (1:1:1 fashion) to 1 of the following 3 groups:

- Group 1: GC therapy (Days 1 and 8 of 21-day cycles) only (n=30)
- Group 2: GC therapy (Days 1 and 8) plus trilaciclib administered intravenous (IV) on Days 1 and 8 of 21-day cycles (n=30)

- Group 3: GC therapy (Days 2 and 9) plus trilaciclib administered IV on Days 1, 2, 8, and 9 of 21-day cycles (n=30)

The study will include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes at the Post-Treatment Visit.

An independent data monitoring committee (DMC) will perform interim reviews of accumulating safety and disposition data approximately every 4 months during the Treatment Phase of the study, depending upon the enrollment rate. The first DMC meeting will occur after approximately the first 20 patients have been enrolled and completed at least 1 cycle. Details of the DMC, including objectives, composition, scope, and frequency, will be described in a DMC charter.

Criteria for Subsequent Cycles and Study Duration

In all 3 groups, study drug administration will continue until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, unacceptable toxicity, withdrawal of consent, or discontinuation by investigator.

Criteria for Day 1/2 of Each Cycle

Patients must meet all of the following criteria to receive the Day 1/2 dose:

- Absolute Neutrophil Count (ANC) ≥ 1.0 × 109/L
- Platelet count ≥ 100 × 109/L
- Nonhematologic toxicities (except alopecia) must be ≤ Grade 2 or have returned to baseline

If the initiation of the next cycle is delayed due to toxicity, the patient should have (at least) weekly visits to follow the toxicity.

Criteria for Day 8/9 of Each Cycle

To receive Day 8/9 dose of each cycle, patients must meet all the following criteria:

- ANC ≥ 1.0 × 109/L
- Platelet count ≥ 75 × 109/L
- Nonhematologic toxicities (except alopecia) must be ≤ Grade 2 or have returned to baseline

If these criteria are not met, the Day 8/9 GC doses should be skipped; no dose reductions or delays are allowed for the Day 8/9 GC doses. If the Day 8/9 GC doses are skipped, the next GC doses become Day 1/2 of the subsequent cycle. There should be at least 7 days between a skipped Day 8/9 dose and the start of the next cycle, i.e., Day 1/2. Note that the criteria for starting Day 1/2 outlined above will now apply to resumption of dosing.

After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the CCI; the Post-Treatment Visit (Day 22); the safety follow-up

phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study, which is to continue until at least 50% of patients have died.

The G1T28-04 study will be completed when the Survival Follow-up Phase has been completed, or upon sponsor termination of the study. The total study duration is at least 19 months, assuming 12 months of accrual, 4 weeks of screening, 4.5 months of treatment (assuming 6 cycles), and 2 months of safety follow-up.

The study scheduled assessments are presented in Table 2 and Table 3 below:

Table 2 Schedule of Assessments for Groups 1 and 2

	Screening	Cycle 1 and Every Odd Cycle[a] (21 days)			Cycle 2 and Every Even Cycle[a] (21 days)			Post-Treatment Visit[b]	Safety Follow-up Phone Call[c]	Survival Follow-up[d]	Post-Treatment Visit + 60 days
Cycle Day	**-28**	**1**	**8**	**15 (±1 day)**	**1**	**8**	**15 (±1 day)**	**22 (last cycle) (+7 days)**	**(+3 days)**	**(±7 days)**	**(±7 days)**
Informed Consent	X										
Demographics	X										
Medical History[e]	X										
Eligibility Evaluation	X										
Performance Status	X	X			X			X			
Physical Exam	X	X			X			X			
Vital Signs	X	X[f]	X[f]		X[f]	X[f]		X			
Height/Weight	X[g]	X			X[g1]						
Clinical Chemistry	X	X[h]			X[h]			X			
Hematology[i]	X	X	X	X	X	X	X	X			X
Urinalysis	X										
ECG	X	X[j]									
Pregnancy test[k]	X	X[k]						X			
CCI											
Tumor Assessment	X[m, m1,m2]	CT/MRI of chest/abdomen Q9 weeks through Week 27 and Q12 weeks thereafter. Also include brain MRI if brain metastases present at baseline. Skeletal lesions identified with baseline bone scan to be followed at scheduled visits using localized CT, MRI, or x-ray [m, m1, m2, m3,m4]							Tumor assessment Q12 weeks to continue in Post-Treatment/Follow-up only if patient discontinues study treatment for reason other than PD and has not initiated subsequent anticancer therapy[m,m4]			
Archival Tumor Tissue	X										
PK[n] (optional)		X[n]									
Trilaciclib[o]		X	X		X	X					
GC therapy[p]		X	X		X	X					
CCI											
Survival Contact[s]										X	
AEs[t]	X										
Con. Medications	X										

AE = adverse event; ECG = 12-lead electrocardiogram; CT = Computed Tomography; FACT-An = Functional Assessment of Cancer Therapy – Anemia quality of life instrument; FACT-B = Functional Assessment of Cancer Therapy –Breast quality of life instrument; MRI = Magnetic Resonance Imaging; PRO = patient reported outcome; PK = pharmacokinetics, GC therapy= Gemcitabine and Carboplatin therapy; PD = progressive disease

a Study therapy will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator.

b Patients will return to the study center for a Post-Treatment Visit on Day 22 (+ 7 days) of their last cycle.

c A safety follow-up contact will be made to each patient at 30 days after the last dose of study treatment to collect AEs and concomitant medications.

d Follow-up should be attempted and documented for each patient that is in the long term Survival Follow-up Phase at least once every 2 months. Patients will be followed for survival until at least 50% of the patients have died. Any anticancer therapies used will be collected.

e Including medical, surgical, radiation history, smoking history, prior systemic anti-cancer therapy, breast cancer history including BRCA classification, screening signs and symptoms within 4 weeks prior to randomization, and medications. Eligibility evaluation and randomization may occur up to 4 days prior to Day 1 Cycle 1 therapy. For all treatment groups, study start is on Cycle 1 Day 1.

f Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be obtained immediately before and after each infusion. Vitals only need to be taken once between each infusion.

g Height will only be measured at the screening visit. Body Surface Area (BSA) will be calculated at Day 1.

g1: BSA (based on actual body weight) will be re-calculated on Day 1 of Cycle 2 and subsequent cycles if weight increases or decreases > 10% from Day 1 of the previous cycle.

h Clinical chemistry (see Protocol Section 11.4.2) may be obtained up to 72 hours prior to Day 1 of each cycle.

i Hematology (see Protocol Section 11.4.2) may be obtained up to 24 hours prior to dosing on Days 1 and 8 of each cycle, Day 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

j Single 12-lead ECGs will be obtained for all patients at screening. For those patients (Groups 1 and 2) who agree to participate in PK sampling will have ECGs completed in triplicate (at least 1 minute apart) at the following additional time points on Day 1 of Cycle 1: predose (prior to trilaciclib) and at 0.5 hour (end of infusion [EOI] of trilaciclib), 2 hours (± 10 minutes) after EOI of trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib. Patients should rest for approximately 5 minutes prior to each ECG assessment. The ECGs should be obtained just prior to PK sampling.

k Female patients of childbearing potential: serum ß-hCG at screening and serum or urine ß-hCG on Day 1 of Cycle 1, Day 1 of every odd cycle, and at the Post-Treatment Visit. A pregnancy test should be obtained within 24 hours of the Cycle 1 Day 1 visit and must be negative to initiate treatment.

CCI [redacted]

m For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI with contrast, where clinically possible, of the chest and abdomen at screening (unless obtained within 28 days of dosing), every 9 weeks ± 7 days (Week 9, Week 18 and Week 27) and then every 12 weeks ± 7 days thereafter, until the occurrence of disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion. If a patient shows a radiological response (complete response [CR] or partial response [PR]), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography is used, it should also be accompanied by spiral CT or MRI.

m1: Radionuclide bone scans shall be performed at screening. Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI or x-ray. Bone scans need not be repeated after baseline unless clinically indicated. Bone scans obtained as standard of care prior to screening will not need to be repeated if performed within 28 days prior to the first dose of study drug(s).

m2. Brain imaging with contrast (by CT or MRI) performed at Screening for all patients. If brain metastases are present at screening, brain imaging shall be done with each protocol-specified tumor assessment. If no metastases are present at screening, imaging does not need to be performed during the study unless clinically indicated or if the subject is neurologically symptomatic.

m3: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks).

m4: For those patients in the Survival Follow-up Phase who have not progressed at the time of study drug discontinuation, radiological tumor assessments will be performed utilizing the same imaging modality used at screening, every 12 weeks ± 7 days from the Post-Treatment Visit until the occurrence of progressive disease, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion.

n Patients who have agreed to participate in the PK analysis will have blood samples collected on Day 1 of Cycle 1 only at the time points specified in Section **Error! Reference source not found.**. **The end of infusion (EOI) sample for trilaciclib should be drawn 2 to 5 minutes prior to the trilaciclib EOI.**

o For Group 2: Trilaciclib will be administered as an IV infusion over 30 (±5) minutes prior to GC chemotherapy on Days 1 and 8 of every 21-day cycle (dosing information, see Protocol Section 8.1). After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO scales; the Post-Treatment Visit (Day 22); the safety follow-up phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study.

p For Group 1: GC therapy will be administered as an IV infusion on Days 1 and 8 of 21-day cycles (dosing information; see Protocol Section 8.1).

For Group 2: GC therapy will be administered as an IV infusion after the trilaciclib infusion (with an interval not greater than 4 hours) on Days 1 and 8 of 21-day cycles (dosing information; see Protocol Section 8.1). Chemotherapy cannot be administered until after completion of the trilaciclib infusion. If trilaciclib in any given cycle is not administered for any reason, do not administer the dose of gemcitabine or carboplatin chemotherapy on that day.

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s Survival follow-up may be a phone contact if subject is not returning to the clinic for tumor assessments.

t AEs will be recorded from the time of informed consent. All AEs should be reported within 30 days of the last dose of study drug, and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

Table 3 Schedule of Assessments for Group 3

	Screen-ing	Cycle 1 and Every Odd Cycle[a] (21 days)					Cycle 2 and Every Even Cycle[a] (21 days)					Post-Treatment Visit[b]	Safety Follow-up Phone Call[c]	Survival Follow-up[d]	Post-Treatment Visit + 60 days
Cycle Day	**-28**	**1**	**2**	**8**	**9**	**15 (±1 day)**	**1**	**2**	**8**	**9**	**15 (±1 day)**	**22 (last cycle) (+7 days)**	**(+3 days)**	**(±7 days)**	**(±7 days)**
Informed Consent	X														
Demographics	X														
Medical History[e]	X														
Eligibility Evaluation	X														
Performance Status	X	X					X					X			
Physical Exam	X	X					X					X			
Vital Signs	X	X[f]	X[f]	X[f]	X[f]		X[f]	X[f]	X[f]	X[f]		X			
Height/Weight	X[g]	X					X[g1]								
Clinical Chemistry	X	X[h]					X[h]					X			
Hematology[i]	X	X		X		X	X		X		X	X			X
Urinalysis	X														
ECG	X		X[j]												
Pregnancy test[k]	X	X[k]										X			
CCI															
Tumor Assessment	X[m,m1,m2]	CT/MRI of chest/abdomen Q9 weeks through Week 27 and Q12 weeks thereafter. Also include brain MRI if brain metastases present at baseline. Skeletal lesions identified with baseline bone scan to be followed at scheduled visits using localized CT, MRI, or x-ray [m, m1, m2, m3, m4]											Tumor assessment Q12 weeks to continue in Post-Treatment/Follow-up only if patient discontinues study treatment for reason other than PD and has not initiated subsequent anticancer therapy[m,m4]			
Archival Tumor Tissue	X														
PK[n] (optional)			X												
Trilaciclib[o]		X	X	X	X		X	X	X	X					
GC therapy[p]			X		X			X		X					
CCI															
Survival contact[s]														X	
AEs[t]	X														
Con. Medications	X														

AE = adverse event; ECG = 12-lead electrocardiogram; CT = Computed Tomography; FACT-An = Functional Assessment of Cancer Therapy – Anemia quality of life instrument; FACT-B = Functional Assessment of Cancer Therapy –Breast quality of life instrument; MRI = Magnetic Resonance Imaging; PRO = patient reported outcome; PK = pharmacokinetics, GC therapy= Gemcitabine and Carboplatin therapy; PD = progressive disease

a Study therapy will continue until disease progression, unacceptable toxicity, or discontinuation by the patient or investigator.

b Patients will return to the study center for a Post-Treatment Visit on Day 22 (+ 7 days) of their last cycle.

c A safety follow-up contact will be made to each patient at 30 days after the last dose of study treatment to collect AEs and concomitant medications.

d Follow-up should be attempted and documented for each patient that is in the long term Survival Follow-up Phase at least once every 2 months. Patients will be followed for survival until at least 50% of the patients have died. Any anticancer therapies used will be collected.

e Including medical, surgical, radiation history, smoking history, prior systemic anti-cancer therapy, breast cancer history including BRCA classification, documentation of tumor diagnosis, screening signs and symptoms within 4 weeks prior to randomization, and medications. Eligibility evaluation and randomization may occur up to 4 days prior to Day 1 Cycle 1 therapy. For all treatment groups, study start is on Cycle 1 Day 1.

f Vital signs (blood pressure, heart rate, respiratory rate and body temperature) will be obtained immediately before and after each infusion. Vitals only need to be taken once between each infusion.

g Height will only be measured at the screening visit. Body Surface Area (BSA) will be calculated at Day 1.

g1: BSA (based on actual body weight) will be re-calculated on Day 1 of Cycle 2 and subsequent cycles if weight increases or decreases >10% from Day 1 of the previous cycle.

h Clinical chemistry (see Protocol Section 11.4.2) may be obtained up to 72 hours prior to Day 1 of each cycle.

i Hematology (see Protocol Section 11.4.2) may be obtained up to 24 hours prior to GC dosing of on Day 2 or Day 9 of each cycle, Day 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.

j Single 12-lead ECGs will be obtained for all patients at screening. Those patients who agree to participate in **PK sampling** will have ECGs completed in triplicate (at least 1 minute apart) at the following additional time points on Day 2 of Cycle 1: predose (prior to trilaciclib) and at 0.5 hour (end of infusion [EOI] of trilaciclib), 2 hours (± 10 minutes) after EOI of trilaciclib, and 5 hours (± 30 minutes) after EOI of trilaciclib. Patients should rest for approximately 5 minutes prior to each ECG assessment. The ECGs should be obtained just prior to PK sampling.

k Female patients of childbearing potential: serum ß-hCG at screening and serum or urine ß-hCG on Day 1 of Cycle 1, Day 1 of every odd cycle, and at the Post-Treatment Visit. A pregnancy test should be performed within 24 hours of the Cycle 1 Day 1 visit and must be negative to initiate treatment.

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m For tumor assessment, all sites of disease should be assessed radiologically by CT or MRI with contrast, where clinically possible, of the chest and abdomen at screening (unless obtained within 28 days of dosing) every 9 weeks ± 7 days (Week 9, Week 18, and Week 27) and then every 12 weeks ± 7 days thereafter, until the occurrence of disease progression, withdrawal of consent, initiation of subsequent anticancer therapy, or study completion. If a patient shows a radiological response (complete response [CR] or partial response [PR]), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. The same method of assessment (CT or MRI) should be used to characterize tumors at screening and at all follow-up assessments. If positron emission tomography is used, it should also be accompanied by spiral CT or MRI.

m1: Radionuclide bone scans shall be performed at screening. Bone scans obtained as standard of care prior to screening will not need to be repeated if performed within 28 days prior to the first dose of study drug(s). Skeletal lesions identified on the bone scan at baseline, which are not visible on the CT or MRI scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI, or x-ray. Bone scans need not be repeated after baseline unless clinically indicated.

m2: Brain imaging with contrast (by CT or MRI) performed at Screening for all patients. If brain metastases are present at screening, brain imaging shall be done with each protocol-specified tumor assessment. If no metastases are present at screening, imaging does not need to be performed during the study unless clinically indicated or if the subject is neurologically symptomatic.

m3: At the Post-Treatment Visit, obtain tumor assessment for patients who have not progressed at the time of study drug discontinuation (may be performed within 4 weeks).

m4: For those patients in the Survival Follow-up Phase who have not progressed at the time of study drug discontinuation, radiological tumor assessments will be performed utilizing the same imaging modality as used at screening, every 12 weeks ± 7 days from the Post-Treatment Visit until the occurrence of progressive disease, withdrawal of consent, initiation of anticancer therapy, or study completion.

n Patients who agree to participate in the PK analysis will have blood samples collected on Day 2 of Cycle 1 at the time points specified in Protocol Section 11.4.2. **The end of infusion (EOI) sample for trilaciclib should be drawn 2 to 5 minutes prior to the trilaciclib EOI.**

o For Group 3: trilaciclib will be administered as an IV infusion over 30 (±5) minutes on Days 1, 2, 8, and 9 of every 21-day cycle. Trilaciclib will be administered prior to GC on Days 2 and 9 (dosing information, see Protocol Section 8.1). The interval between doses of trilaciclib on successive days should not be greater than 28 hours. After discontinuation of study drug, patients should be strongly encouraged to complete all scheduled assessments through the end of their current 21-day treatment cycle, including the PRO scales; the Post-Treatment Visit (Day 22); the safety follow-up phone call at 30 days after the last dose of study treatment; and the Survival Follow-up Phase of the study.

p For Group 3: GC therapy will be administered as an IV infusion after the trilaciclib infusion (with an interval not greater than 4 hours) on Days 2 and 9 of 21-day cycles (dosing information; see Protocol Section 8.1). Chemotherapy cannot be administered until after completion of the trilaciclib infusion. If trilaciclib in any given cycle is not administered for any reason, do not administer the dose of gemcitabine or carboplatin chemotherapy on that day.

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s Survival follow-up may be a phone contact if subject is not returning to the clinic for tumor assessments.

t AEs will be recorded from the time of informed consent. All AEs should be reported within 30 days of the last dose of study drug, and followed until they are resolved, have returned to baseline, or it is deemed that further recovery is unlikely.

2.3. Number of Patients

Overall, approximately 90 patients will be enrolled in the study. The 90 patients will be randomly assigned (1:1:1) to 1 of 3 groups.

The sample size is not determined from a statistical perspective, but rather is based on clinical feasibility. Approximately 90 patients will be enrolled into the study (30 per treatment group). With 30 patients, the precision for point estimates in each arm is as follows: the maximum 95% confidence interval (CI) width for binary endpoints based on Wilson score intervals is the observed proportion +/- 0.167. The 95% CI width for continuous endpoints using the t-distribution are the observed mean +/- 0.373*standard deviation of the endpoint.

With the changes to the protocol detailed in this SAP, the sample size calculation is now based on demonstrating the superiority of Group 3 (GC + Trilaciclib Day 1/2 and 8/9) and Group 1 (GC therapy alone) with respect to at least one of the primary endpoints.

With the changes, the overall type I error rate is now 0.025 (1-sided) and the type II error rate used to compute sample size is 0.10 (corresponding to 90% power).

To maintain the overall type I error rate, by using the most conservative Bonferroni procedure for the 2 primary endpoints, a 1-sided individualized type I error rate 0.025/2 = 0.0125 is assigned to each outcome variable in the sample size calculation. Assuming a common standard deviation of 2.5, a true difference in the duration of severe (Grade 4) neutropenia in Cycle 1 of at least 3 days between the Group 3 and Group 1 requires, 38 evaluable patients (19 per treatment arm in Groups 1 and 3). This implies that 60 patients need to be randomized for all 3 groups assuming a 95% evaluability rate. For occurrence endpoints (occurrence of severe (Grade 4) neutropenia, assuming its proportion of 45% for Group 1, testing for an absolute reduction of 41% to 4% with Group 3 would require a sample size of at least 96 patients (32 per treatment arm in Groups 1 and 3). Assuming a 95% evaluability rate, at least 102 patients need to be randomized for all 3 groups to complete the study. Therefore, the final adjusted sample size is 102 to account for the evaluation of 2 primary endpoints. All calculations were carried out using the POWER procedure in SAS® version 9.4.

The study will be conducted at up to 50 centers in North America and Europe.

3. ANALYSIS SETS

3.1. Definition of Analysis Sets

Data analyses will be based on the four analysis sets defined below. Analysis sets, including exclusions based on key deviations, will be reviewed and approved by G1 Therapeutics prior to the study unblinding. See Section 7 for the changes from the protocol defined analysis sets.

3.1.1. Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set includes all randomized patients. Analyses using the ITT will be conducted on the basis of the assigned treatment. All myelopreservation efficacy analyses will be assessed using the ITT. The ITT will also be used for analyses of progression-free survival (PFS) and overall survival (OS).

3.1.2. Modified ITT Analysis Set

A modified ITT (mITT) analysis set is a subset of the ITT analysis set and will only include the ITT patients who received at least 1 dose of study drug (gemcitabine, carboplatin, or trilaciclib). Supportive sensitivity analyses will be conducted based on the mITT analysis set for primary and key secondary efficacy endpoints to evaluate the robustness of the results. Analyses using the mITT will be conducted on the basis of the assigned treatment. mITT will be used for sensitivity of select efficacy analyses.

3.1.3. Safety Analysis Set

The safety analysis set includes all enrolled patients who received at least 1 dose of study drug (gemcitabine, carboplatin, or trilaciclib). Analyses using the safety analysis set will be conducted on the basis of the actual treatment received. All safety analyses will be assessed using the safety population.

3.1.4. Per Protocol (PP) Analysis Set

The per-protocol (PP) analysis set is a subset of mITT analysis set and will include only those patients who have no key protocol deviations (as described in Section 3.2) and who received the treatment to which they were randomized. For any patients who received the wrong treatment during any part of the study, their data will be excluded from the PP analysis set. PP analysis set may be used to analyze selected endpoints to test the robustness of results.

3.1.5. Response Evaluable Analysis Set

The Response Evaluable Analysis Set will include all patients who are in the mITT, have measurable disease (target lesions) at the baseline tumor assessment, and either (i) have at least 1 post-baseline tumor assessment, (ii) have clinical progression as noted by the investigator before their first post-baseline tumor scan, or (iii) have died due to disease progression before their first post-baseline tumor scan. The response evaluable analysis set will be used for sensitivity analyses of tumor response.

3.2. Protocol Deviations

Certain protocol deviations are key in that they may affect the ability to assess the safety and efficacy of study drug. Patients with key deviations will be excluded from the PP analysis set.

All patients who meet the definition of the ITT/mITT analysis sets will be included in the ITT/mITT analysis set regardless of these deviations.

The criteria for inclusion in the PP set will be finalized and documented prior to locking data for the study.

If a patient is randomized, but fails to receive treatment, the reason for not receiving treatment will be noted in the CSR. Any such patients who are not treated will be excluded from the mITT, safety, response evaluable, and PP analysis sets but will be included in the ITT and in the patient listings for the CSR.

If the wrong treatment is administered to a patient, and the reason for the incorrect treatment is documented, this will be noted in the CSR and the patient's data included in the Safety Analysis Set based on the actual treatment received. Additional protocol deviations will be reviewed in a data review meeting to classify protocol deviations as non-key or key, and to discuss the potential impact on statistical analysis.

4. PROSPECTIVELY DEFINED ANALYSES

As outlined in the protocol, trilaciclib is an IV cyclin dependent kinase (CDK) 4/6 inhibitor being evaluated for its ability to decrease chemotherapy-induced myelosuppression when administered in combination with cytotoxic chemotherapy. Unlike granulocyte-colony stimulating factor (GCSF), which stimulates production of neutrophils, and transfusions, which only replace red blood cell (RBC) or platelets, trilaciclib is hypothesized to facilitate myelopreservation of all hematopoietic lineages including neutrophils, RBC, platelets, lymphocytes, etc.

Based on the mechanism of action, it is also hypothesized that the effects of trilaciclib-induced myelopreservation may be more obvious after patients receive repeated cycles of chemotherapy. For example, TNBC patients treated with gemcitabine and carboplatin often have more dosing reductions and hematologic-related adverse events (AEs) after multiple cycles due to repeated damage to the bone marrow. In contrast, addition of trilaciclib to gemcitabine and carboplatin is theorized to counteract the chemotherapy-induced damage and allow patients to receive multiple cycles of therapy with less dose reductions and fewer hematologic-related AEs.

To capture these two aspects of trilaciclib benefit, the following analyses are prospectively proposed in Table 4 and their associated endpoint derivation and analysis methods will be detailed in Sections 5.1 and 6.2.7 with the multiplicity adjustments described in Section 6.2.7.1.4.

Table 4 Prospectively Defined Analyses

Occurrence (proportion of patients) of severe (Grade 4) neutropenia
Duration of severe (Grade 4) neutropenia
Occurrence (proportion of patients) of RBC transfusions on/after 5 weeks
Occurrence (proportion of patients) of GCSF administration
Occurrence (proportion of patients) of Platelet transfusion
Cumulative incidence of major adverse hematologic events (MAHE) which is defined to include components as the following: • All-cause hospitalizations • All-cause dose reductions • Febrile neutropenia • Prolonged severe (Grade 4) neutropenia (duration > 5 days) • RBC transfusions on/after 5 weeks • Platelet transfusions
All-cause hospitalizations in the MAHE composite
All-cause dose reductions in the MAHE composite
Febrile neutropenia in the MAHE composite
Prolonged severe (Grade 4) neutropenia in the MAHE composite
RBC transfusions on/after 5 weeks in the MAHE composite
Platelet transfusions in the MAHE composite

RBC = Red Blood Cell; GCSF = granulocyte-colony stimulating factor;

5. PRIMARY AND SECONDARY ENDPOINTS

The following general definitions will be applied to all endpoints derivation unless otherwise specified.

Term	Definition
Severe Neutropenia (SVN)	ANC lab value that meets the common terminology criteria for adverse events (CTCAE) criteria for ≥ Grade 4 toxicity
Cycle baseline	The last non-missing value within the window starting from 3 days prior to the date/time of study drug administration on Day 1 of Cycle 1 and 1 day prior to Day 1 of each subsequent cycle (i.e. Cycle 2, Cycle 3, etc.); must be prior to the time of study drug administration
Cycle nadir	The lowest value for a given hematologic parameter that occurs between start of cycle and end of cycle and is less than the cycle baseline.
Duration of cycle	Total number of days from start of cycle to end of cycle, that is, date of end of a cycle - date of start of cycle + 1.
End of cycle*	Day 1 of the subsequent cycle. For example, the end of cycle for Cycle 1 is Day 1 of Cycle 2. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as Day 30 after the first dose of the cycle.
Start of cycle	Day 1 of each cycle starts with the administration of study drug(s) (gemcitabine, carboplatin or trilaciclib)
Start of study	Date of randomization
Study baseline	The last non-missing value prior to, or on the date of administration of study drug(s) (gemcitabine, carboplatin or trilaciclib); must be prior to the time of study drug administration
Change from baseline	Calculated as the post-baseline value minus the baseline value. If the baseline value is missing for a particular endpoint, change from baseline will be missing.
Treatment period	Between the date of randomization and end of cycle for the last cycle

* For various hematologic parameter analyses, the last assessment prior to end of cycle will be utilized in the analyses. Situations where this applies will be indicated as such.

5.1. Efficacy Endpoints

5.1.1. Primary Endpoints

5.1.1.1. Occurrence of Severe (Grade 4) Neutropenia

For the treatment period, the total number of SVN events is the number of cycles where at least one ANC value is $< 0.5 \times 10^9$/L. For example, if Cycle 2 has two ANC values that are both $< 0.5 \times 10^9$/L, this only counts as one event. If a patient did not have any SVN events, the value of 0 will be assigned to that patient. Unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation.

Hence, any occurrence of an SVN during the treatment period is defined as a binary variable (Yes or No); Yes, if total number of cycles with SVN ≥ 1 is observed, No for other scenarios.

5.1.1.2. Duration of Severe (Grade 4) Neutropenia (DSN)

There will be two different strategies for assessing DSN in each cycle. Both strategies will be applied to derive the DSN, with strategy 1 considered as the primary, and strategy 2 being supportive sensitivity analyses. The DSN in Cycle 1 is considered for this primary endpoint.

5.1.1.2.1 Strategy 1: Without Imputation of Missing ANC Values

Within each cycle, the DSN (days) is defined as the number of days from the date of first ANC value of $<0.5\times10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5\times10^9$/L that meets the following criteria: (1) occurs after the ANC value of $<0.5\times10^9$/L and (2) no other ANC values $<0.5\times10^9$/L occur between this day and end of cycle. DSN is set to 0 in patients who did not experience SVN in a cycle. Any unscheduled data and the actual assessment date (rather than visit date) will be included in the derivation. The following rules will be applied in the calculation:

(i) For a cycle where the SVN event does not resolve by end of the cycle, DSN will be assigned as above except the end date will be the end of cycle.

(ii) For a cycle where the patient dies, during the SVN event, DSN will be assigned as above except the end date will be the date of death.

(iii) For a cycle where the patient withdraws consent or is lost to follow-up during the SVN event, DSN will be assigned as above except the end date will be the date of the last ANC assessment prior to the end of study.

5.1.1.2.2 Strategy 2: Without Imputation, Censoring Unresolved SVN

Within each cycle, DSN (days) is defined as the number of days from the date of first ANC value of $<0.5 \times 10^9$/L observed between start of cycle and end of cycle, to the date of first ANC value $\geq 0.5 \times 10^9$/L that meets the following criteria: (1) occurs after the ANC value of $<0.5 \times 10^9$/L and (2) no other ANC values $<0.5 \times 10^9$/L occur between this day and end of cycle. The following censoring rules will be applied in the calculation:

(iv) For a cycle where the SVN event does not resolve by end of the cycle, DSN will be assigned as above except the end date will be the earlier of end of cycle or date of last contact.

(v) For a cycle where the patient dies, withdraws consent, or is lost to follow-up during the SVN event, DSN will be assigned as above except the end date will be the date of the last ANC assessment prior to the end of study.

For the treatment period, the overall DSN (days) is the median value among the DSN (days) from all cycles. The following data handling conventions will apply:

- For those patients where all event duration values are derived from cycles with censored data, the median value for that patient will be the median censored value. It will be a considered a censored value;
- For those patients where a subset of event duration values are derived from cycles with censored data, the median value for that patient will be estimated using the Kaplan-Meier method. It will be considered as an observed value (i.e. no censored value);

- For those patients where the median event duration cannot be derived (e.g. ≤ 2 values), the longest event duration amongst all the cycles will be used regardless of censoring, but the corresponding censoring flag will be carried over for analysis.

5.1.2. Key Secondary Endpoints

5.1.2.1. Occurrence of RBC Transfusions

Each RBC transfusion with a unique start date on/after 5 weeks on study during the treatment period will be defined as a separate event, and an additional set of all events occurring during the treatment period will be examined for sensitivity.

Occurrence of a RBC transfusion during the treatment period is defined as a binary variable (Yes or No); Yes if total number of RBC transfusion ≥ 1 is observed, No for other scenarios.

5.1.2.2. Occurrence of GCSF Administrations

Administration of GCSF is collected throughout the treatment period. Those cycles where GCSF is administered concurrently will be identified by comparing the start and stop dates of each administration of GCSF to the start of cycle and end of cycle. If any of the dates of administration of GCSF overlap with any dates between the start of cycle and end of cycle, that cycle will be considered as having GCSF administered. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

For the treatment period, the total number GCSF administrations is the number of cycles in which there is at least one GCSF dose administered. If a patient did not have any GCSF use, the value of 0 will be assigned to that patient. The number of cycles where GCSF was NOT given is calculated as total number of treatment cycles received – total number of cycles where GCSF was administered.

Therefore, any occurrence of a GCSF administration during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with GCSF administration ≥ 1 is observed, No for other scenarios.

5.1.2.3. Occurrence of Platelet Transfusions

Each platelet transfusion with a unique start date during the treatment period will be defined as separate event.

Occurrence of a platelet transfusion during the treatment period is defined as a binary variable (Yes or No); Yes if total number of platelet transfusion ≥ 1 is observed, No for other scenarios.

5.1.2.4. All-Cause Dose Reductions (number of events)

Dose (mg/m^2) reductions are not permitted for trilaciclib. Dose reductions for carboplatin and gemcitabine are derived from changes in the planned dose on the dosing page.

Up to 3 total dose reductions are allowed for carboplatin and gemcitabine, each will be counted as a unique event. For more details see Section 5.2.1.4

5.1.2.5. Overall Survival

Although OS is a key secondary endpoint, OS will be analyzed with a descriptive intention and will not be factored into multiplicity adjustment as described in Section 6.2.7.1.4. That is, no formal statistical testing will be planned. The analysis of OS will be primarily aimed at showing lack of harm from trilaciclib.

Overall survival is calculated as the time (months) from date of randomization to the date of death due to any cause. Patients who do not die during the study will be censored at the date last known to be alive. Patients lacking data beyond the date of randomization will have their survival time censored at date of randomization. OS will not be censored if a patient receives other anti-tumor treatments after the study drugs.

5.1.3. Supportive Secondary Endpoints

5.1.3.1. Total Number of Major Adverse Hematologic Events (MAHE)

As a composite measure of trilaciclib effect, MAHE is based on a combination of individual components specified in Table 5, which also include details about the derivation or data source for each component. For each component of composite MAHE, its number of events is derived as the number of episodes with a unique start date during the treatment period between the date of randomization and the end of the last cycle (i.e. last cycle of GC only or trilaciclib plus GC). A patient with absence of an episode will be assigned a value of 0 to the number of events for this component. Then, the total number of MAHE during the treatment period is obtained as the summation over all components of composite MAHE during the treatment period.

Table 5 Component of MAHE and the Suggested Data Source/Derivation Algorithm

Seq #	Component of MAHE	Details
1	All-cause hospitalizations	Each hospitalization is captured in the AE data of the electronic database. Each recorded Preferred Term (PT) with a unique start date will be counted as an event. The event terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1.
2	All-cause dose reductions	Detailed in Section 5.1.2.4**Error! Reference source not found.**
3	Febrile neutropenia	Detailed in Section 5.1.3.9**Error! Reference source not found.**
4	Prolonged severe (Grade 4) neutropenia (duration > 5 days)	Detailed in Section 5.1.1.2.1. Each cycle with a duration greater than 5 days will be counted as an event with the date of the first grade 4 lab value defined as the start date for the time-to-first event analysis.
5	RBC transfusion on/after 5 weeks	Detailed in Section 5.1.2.1
6	Platelet transfusion	Detailed in Section 5.1.2.3.

A patient with absence of any episode of MAHE will be assigned a value of 0 for the total number of MAHE. Additionally, a sensitivity analysis will be done for dose reductions and RBC transfusions on/after 5 weeks, that excludes patients who do not start a second cycle of treatment.

Time to first occurrence of a MAHE will be used as a sensitivity analysis in support of the total number of MAHE. It is defined as the first time to observe an event among all the components, starting from the date of randomization. Therefore, for a patient with presence of MAHE, time (months) to first occurrence of a MAHE will be the minimum among the 6 potentially derived duration (i.e. calculated as (date of first occurrence of a MAHE component event – date of randomization + 1)/30). A patient without any MAHE will be censored at the end of the last cycle (i.e. last cycle of GC only or trilaciclib plus GC), death, end of study, or date of last contact, whichever is earlier.

5.1.3.1.1 All-Cause Hospitalizations

See Section 5.1.3.1.

5.1.3.1.2 Prolonged severe (Grade 4) neutropenia (duration > 5 days)

See Section 5.1.3.1.

5.1.3.2. Best Overall Response, Duration of Response, and Progression-Free Survival

For tumor assessment, all sites of disease will be assessed radiologically by CT or MRI at screening, every 6-12 weeks thereafter as determined by the protocol, until the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. At each tumor assessment visit, the overall visit response by RECIST will be determined two ways: (1) derived programmatically using the information from target lesions (TL), non-target lesions (NTLs) and new lesions as entered into the eCRF, and (2) by the investigator and collected in the eCRF.

For all patients, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST Version 1.1 and the best overall response (BOR).

5.1.3.2.1 Target Lesions (TLs)

Measurable disease is defined as having at least one measurable lesion which is

- ≥10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI); or
- ≥10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); or
- ≥ 20 mm by chest X-ray.

Previously irradiated lesions (or lesions treated with loco-regional therapies) may be considered measurable if unequivocal growth of the lesion has been demonstrated. A patient can have a maximum of 5 measurable lesions representative of all involved organs (maximum of 2 lesions per organ, both the lymph node and skin will be considered as a single organ) recorded at baseline and these are referred to as target lesions. If more than one baseline scan is recorded then measurements from the one that is closest to start of treatment will be used to define the baseline sum of TLs. Table 6 gives definition of TL visit responses.

Table 6 Definition of TL Visit Responses

Visit Reponses	Description
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of target lesions and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters (i.e. nadir) since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a target lesion response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

If any target lesion measurements are missing then the target lesion visit response is Not Evaluable (NE). The overall visit response will also be NE, unless there is a progression of non-target lesions or new lesions, in which case the response will be PD.

TL too small to measure

If a target lesion becomes too small to measure a value of 5mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured.

Lesions that split

If a TL splits, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If target lesions merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 cm.

Change in method of assessment of target lesions

CT, MRI, chest x-ray and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination and, chest x-ray only used in special cases. If a change in method of assessment occurs between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

5.1.3.2.2 Non-Target Lesions (NTLs) and New Lesions

The non-target lesion response will be based on the Investigator's assessment of NTLs as Table 7:

Table 7 Definition of NTLs Visit Responses

Visit Reponses	Description
CR	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10mm short axis).
PD	Unequivocal progression of existing NTLs, which may be due to an important progression in one lesion only or in several lesions
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression
NE	Only relevant when one or some of the NTLs have not been assessed and in the Investigator's opinion they are not able to provide an evaluable overall NTL assessment.

New lesions

New lesions will be identified via a separate eCRF page. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression, so the overall visit response will be PD irrespective of the TL and NTL responses.

5.1.3.2.3 Time Point Response (TPR)

Table 8 and Table 9 define how the previously defined TL and NTL visit responses will be combined with new lesion information to give a TPR. The possible TPRs at a visit are CR, PR, SD, Non-CR/Non-PD, PD, and NE.

Table 8 Evaluation of Time Point Response: Patients with Baseline Target Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/not all evaluated	No	PR
SD	Non-PD/not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable

Table 9 Evaluation of Time Point Response: Patients without Baseline Target Lesions

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

At each visit, patients will be programmatically assigned a RECIST Version 1.1 TPR of CR, PR, SD, Non-CR/Non-PD, PD or NE depending on the status of their disease compared to baseline and previous assessments as discussed in the Sections 5.1.3.2.1 and 5.1.3.2.2.

For a scheduled tumor scan assessment, it is expected that there will be a variation for the actual timing of scans among target, non-target, and new lesions. In assigning a date for the derived overall assessment at a visit, the earliest date collected at that visit will be used. Within a grouped timepoint, if there are multiple assessments on different dates for the *same* target lesions, the last assessment will be used.

5.1.3.2.4 Best Overall Response (BOR) and Duration of Response (DOR)

BOR will be determined using TPRs up until the last evaluable TPR prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier. BOR will not be derived for those patients who do not have measurable target lesions.

A patient's BOR will be determined based on Table 10. For data-driven scenarios which may not be covered by Table 10, the BOR will be reviewed and determined by the medical advisors and statisticians prior to locking the database.

For patients who progress and subsequently have a response, the best overall response is only derived from assessments up to and including the time of the progression (i.e., it will not include the response after the patient has progressed).

There are two ways of assigning BOR for a patient when the minimum interval for confirmation of CR and PR is not satisfied or if there are no confirmatory scans for CR and PR:

- Adding two more response categories as: unconfirmed CR, unconfirmed PR;
- Assigning BOR as SD, that is, both the unconfirmed CR and unconfirmed PR will be SD.

Both ways of assigning BOR will be implemented.

The number and percentage of patients in each category of derived BOR (Confirmed CR, Confirmed PR, SD, PD, or NE) will be summarized.

Table 10 Best Overall Response When Confirmation of CR and PR are Required [a]

First TPR	Second TPR	Best overall response*^ for ORR	Best Overall Response for $ORR_{UNCONFIRMED}$
CR	CR	CR	CR
CR	PR	SD [b] or PD	Unconfirmed CR
CR	SD	SD [b] or PD	Unconfirmed CR
CR	PD	SD [b] or PD	Unconfirmed CR
CR	NE or NA	SD [c] or NE or NA	Unconfirmed CR
PR	CR	PR	Unconfirmed CR
PR	PR	PR	PR
PR	SD	SD [d]	Unconfirmed PR
PR	PD	SD [b] or PD	Unconfirmed PR
PR	NE or NA	SD [c] or NE or NA	Unconfirmed PR
NE	NE	NE	NE
NE	CR	SD	Unconfirmed CR
NE	PR	SD	Unconfirmed PR
NE	SD	SD	SD
NE or NA	PD	PD	PD
SD	PD	SD [b] or PD	SD [b] or PD
SD	CR	SD	SD
SD	PR	SD	SD
SD	SD	SD	SD
SD	NE or NA	SD [c] or NE or NA	SD [c] or NE
PD	No further evaluation	PD	PD
Non-CR/Non-PD	PD	PD	PD
Non-CR/Non-PD	CR	Non-CR/Non-PD	Non-CR/Non-PD
Non-CR/Non-PD	PR	Non-CR/Non-PD	Non-CR/Non-PD
Non-CR/Non-PD	SD	Non-CR/Non-PD	Non-CR/Non-PD
Non-CR/Non-PD	NE or NA	NE or NA	NE

CR = complete response, PR= partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not available, ORR = Objective Response Rate

a. The minimum interval for confirmation of CR and PR is 4 weeks.

b. Best response will be SD if the first time point overall response is after 35 days on study. Otherwise, the best response will be PD.

c. Best response will be SD if the first time point overall response if after 35 days on study. Otherwise, the best response will be NE.

d. Best response will be SD provided the criteria for PD have not been met from the first to second assessment.

* A best overall response of SD can only be made after the subject is on study for a minimum of 35 days (counted from Cycle 1 Day 1). If the subject is on study for less than 35 days, any tumor assessment indicating stable disease before this time period will have a best response of NE unless PD is identified.

^Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE (e.g., CR NE CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (e.g., PR NE PR or PR SD PR). However, only one (1) intervening NE or SD will be allowed between PRs for confirmation. Note: in the following scenario, PR SD NE PR, the second PR is not a confirmation of the first PR.

Objective response rate (ORR) will be calculated using two methods:

Method #1: ORR will be calculated using a strict interpretation of RECIST Version 1.1. Objective response will be derived as no/yes (0/1) variable. Patients with a BOR of confirmed CR or PR will be assigned 'Yes'. Patients not having a BOR of confirmed CR or PR will be assigned 'No'. Hence, ORR is defined as the proportion of patients with objective response being "Yes".

Method #2: $ORR_{UNCONFIRMED}$ will be calculated using all responses regardless of confirmation. Objective response will be derived as no/yes (0/1) variable. Patients with a BOR of confirmed CR, confirmed PR, unconfirmed CR or unconfirmed PR will be assigned "Yes". All patients with other BOR values will be assigned "No". Hence, $ORR_{UNCONFIRMED}$ is defined as the proportion of patients with objective response being "Yes".

Duration of Response (DOR) is the time between first response by RECIST Version 1.1 of CR or PR and the first date that progressive disease is documented by RECIST Version 1.1, or death. Patients who do not experience PD or death will be censored at the last tumor assessment date. Only those patients with confirmed responses will be included in this analysis. Censoring will follow the rules outlined below for PFS in Section 5.1.3.2.5.

Clinical benefit rate (CBR) is defined as the proportion of patients with a BOR of confirmed CR, confirmed PR, or SD.

ORR, $ORR_{UNCONFIRMED}$, DOR and CBR will be calculated using the derived responses and investigator responses.

5.1.3.2.5 Progression-free Survival

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented.

Hence, progression-free survival (PFS) is defined as the time (months) from date of randomization until date of documented disease progression or death due to any cause, whichever comes first. More specifically, PFS will be determined using all the assessment data up until the last evaluable visit prior to or on the date of (i) disease progression as defined by RECIST Version 1.1 (Eisenhauer et al, 2009); or (ii) withdrawal of consent; or (iii) receiving subsequent anti-cancer therapy, whichever is earlier.

PFS will be calculated using derived responses and progression by RECIST Version 1.1 (whichever comes first) will be considered.

Death, regardless of cause, is always considered as a PD event. The detailed censoring rules for the analysis are summarized in Table 11.

Table 11 Assignment of Progression or Censoring Based on Radiological Assessment

Situation	Date of Progression or Censoring	Outcome
No Baseline assessment	Date of randomization	Censored
No progression - treatment not started	Date of randomization	Censored
No progression	Date of last adequate radiological disease assessment	Censored
Treatment discontinuation for reasons other than disease progression	Date of last adequate radiological disease assessment with no documented progression	Censored
New anticancer treatment started prior to documented disease progression	Date of last adequate radiologic assessment no later than the initiation of new anticancer treatment	Censored
Disease progression per RECIST Version 1.1	Date of the first reported progression	Progressed
Death without a PD	Date of death	Progressed
Determination of clinical progression per the investigator	Date of the investigator assigned PD	Progressed [a]

[a] For the primary derivation of PFS, the clinical progression will not be included (i.e. it will only be based on radiologic progression), but it will be incorporated as a separate derivation of PFS, and its analysis will be considered to be supportive.
Note: An adequate radiologic assessment is defined as an assessment where the Investigator determined radiological response is CR, PR, SD, or PD. If PD and new anti-cancer therapy occur on the same day, will assume that the progression was documented first, *e.g.* outcome is progression and the date is the date of the assessment of progression.

5.1.3.3. Occurrence of Grade 3 and 4 Hematologic Toxicities

Hematologic toxicities events are defined as any cycle where any hematologic lab value occurs that meets the CTCAE toxicity grade criteria for ≥ Grade 3 and the value is treatment emergent. For details on which parameters are included and the definition of treatment emergent see Section 5.2.4.

For the treatment period, the total number of hematologic toxicity events is the number of cycles in which there is at least one hematologic toxicity event. If a patient did not have any hematologic toxicity events, the value of 0 will be assigned to that patient. The number of cycles without hematologic toxicity events is calculated as total number of treatment cycles received – total number of cycles with a hematologic toxicity event.

Therefore, any occurrence of a hematologic toxicity event during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with a hematologic toxicity event ≥ 1 is observed, No for other scenarios.

5.1.3.4. ANC Nadir by Cycle

See table in Section 5 for the definition of cycle nadir.

5.1.3.5. ANC, Platelet Count, Absolute Lymphocyte Counts (ALC), and Hemoglobin Change over Time

For the hematologic parameters consisting of ANC, hemoglobin, platelet count, and ALC, the observed lab values in each windowed visit as detailed in Section 6.1.3 will be appropriately identified for further analysis.

5.1.3.6. Occurrence of Erythropoiesis Stimulating Agent (ESA) Administrations

Administration of ESAs is collected throughout the treatment period. Those cycles where ESAs are administered concurrently will be identified by comparing the start and stop dates of each ESA to the start of cycle and end of cycle. If any of the dates of administration of an ESA overlap with any dates between the start of cycle and end of cycle, that cycle will be considered as having an ESA administered. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

For the treatment period, the total number of ESA administrations is the total number of cycles in which there is at least one ESA dose administered;. If a patient did not receive an ESA, the value of 0 will be assigned to that patient. The number of cycles where ESAs were NOT given is calculated as total number of treatment cycles received – total number of cycles where ESAs were administered.

Therefore, any occurrence of an ESA administration during the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with ESA administration ≥ 1 is observed, No for other scenarios.

5.1.3.7. Occurrence of IV Antibiotic Uses

IV antibiotic administration is collected with concomitant medications which are coded using World Health Organization Drug Dictionary (WHO-DD) Version Sep2017. The criteria for identifying an IV antibiotic administration event is

- If the Therapeutic subgroup from WHO-DD Version Sep2017 (i.e. TEXT2 for CODE2) takes value “ANTIBACTERIALS FOR SYSTEMIC USE”, and
- The route of medication is “intravenous” or the route is “other” with the detailed specification as “IVPB”.

Each IV antibiotic with a unique start date during the treatment period will be defined as a separate event. Data handling conventions for missing start and stop dates are described in Section 6.2.5.

Occurrence of an IV antibiotics administration during the treatment period is defined as a binary variable (Yes or No); Yes if total number of IV antibiotics administration ≥ 1 is observed, No for other scenarios.

5.1.3.8. Occurrence of Infection Serious Adverse Events (SAEs)

Each infection SAE is captured in the electronic database. The event terms are coded using the MedDRA Version 20.1. The criterion for identifying the proper infection SAE records is as

follows: if the system organ class (SOC) from MedDRA takes value "INFECTIONS AND INFESTATIONS", and the AE is a serious event.

Each infection SAE with a unique start date during the treatment period will be defined as separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.2.

Any occurrence of an infection SAE during the treatment period is defined as a binary variable (Yes or No); Yes if total number of infection SAE events ≥ 1 is observed, No for other scenarios.

5.1.3.9. Occurrence Febrile Neutropenia

Each febrile neutropenia event is captured in AE data of electronic database, and "FEBRILE NEUTROPENIA" is a preferred term which can be used to identify the proper AE records. The event terms are coded using the MedDRA Version 20.1.

Each febrile neutropenia event with a unique start date during the treatment period will be defined as a separate event. Data handling conventions for missing start and stop dates for AEs are described in Section 5.2.2.

Any occurrence of a febrile neutropenia event during the treatment period is defined as a binary variable (Yes or No); Yes if total number of febrile neutropenia events ≥ 1 is observed, No for other scenarios.

5.1.3.10. Occurrence of Grade 4 and Grade 3 or 4 Thrombocytopenia

Hematologic toxicities events are defined as any cycle where any hematologic lab value occurs that meets the CTCAE toxicity grade criteria for ≥ Grade 3 and the value is treatment emergent. For details on which parameters are included and the definition of treatment emergent see Section 5.2.4.

For the treatment period, the total number of hematologic toxicity events is the number of cycles in which there is at least one hematologic toxicity event. If a patient did not have any hematologic toxicity events, the value of 0 will be assigned to that patient. The number of cycles without hematologic toxicity events is calculated as total number of treatment cycles received – total number of cycles with a hematologic toxicity event.

Therefore, any occurrence of a hematologic toxicity event during a cycle or the treatment period is defined as a binary variable (Yes or No); Yes if total number of cycles with a hematologic toxicity event ≥ 1 is observed, No for other scenarios.

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[redacted]

5.2. Safety Endpoints

5.2.1. Chemotherapy Exposure Endpoints

5.2.1.1. Duration of Exposure

Duration of exposure (days) = First dose date of study drug from the last cycle – first dose date of study drug + 21.

5.2.1.2. Number of Cycles Received

Patients are considered to have started a cycle if they have received at least one dose of any study drug (carboplatin, gemcitabine, or trilaciclib). In addition to the numeric summary for the number of cycles, the number of cycles will be categorized as 1, 2, 3 or 4, 5 or 6, and > 6.

5.2.1.3. Dose Intensity and Cumulative Dose

Algorithms for calculating parameters relevant to the dose exposure and intensity are included in Table 12.

Table 12 Algorithms for Calculating Parameters Relevant to the Dose Exposure and Intensity

Parameter	Trilaciclib	Gemcitabine	Carboplatin
Dosing schedule per protocol	Group 2: 240 mg/m^2 IV on Days 1 and 8 of a 21-day cycle Group 3: 240 mg/m^2 IV on Days 1, 2, 8 and 9 of a 21-day cycle	Group 1 & 2: 1000 mg/m^2 IV on Days 1, 8 of a 21-day cycle Group 3: 1000 mg/m^2 IV on Days 2, 9 of a 21-day cycle	Group 1 & 2: AUC 2 IV on Days 1, 8 of a 21-day cycle Group 3: AUC 2 IV on Days 2, 9 of a 21-day cycle
Dose by cycle	Total dose administered on Days 1 and 8 (Group 2) or Days 1, 2, 8 and 9 (Group 3) (mg) /most recent BSA (m^2) [(mg/m^2)]	Total dose administered on Days 1 and 8 (Group 2) or Days 2 and 9 (Group 3) (mg)/most recent BSA (m^2) [(mg/m^2)]	Total dose administered on Days 1 and 8 (Group 2) or Days 2 and 9 (Group 3) (Prescribed AUC and actual dose in mg)
Cumulative dose	Sum of the total doses by cycle (mg/m^2) administered to a patient in the duration of exposure, i.e. total number of cycles received [(mg/m^2)]	Sum of the total doses by cycle (mg/m^2) administered to a patient in the duration of exposure, i.e. total number of cycles received [(mg/m^2)]	Sum of the total doses by cycle (AUC) administered to a patient in the duration of exposure, i.e. total number of cycles received (in total prescribed AUC)
Dose intensity	Cumulative dose (mg/m^2) / (duration of exposure / 7) [(mg/m^2/week)]	Cumulative Dose (mg/m^2) / (duration of exposure / 7) [(mg/m^2/week)]	Cumulative Dose (total prescribed AUC) / (duration of exposure / 7) [AUC/ week]
Relative dose intensity (%)	Group 2:100 * [Dose intensity (mg/m^2/week) / (480 /3 (mg/m^2/week)] Group 3: 100 * [Dose intensity (mg/m^2/week) / (960 /3 (mg/m^2/week)]	100 * [Dose intensity (mg/m^2/week) / (2000 /3 (mg/m^2/week)]	100 * [Dose intensity (AUC/week) / (4/3) (AUC/week)]
Relative Dose (%)	Group 2:100 * [Cumulative dose (mg/m^2) / (480 × number of cycles (mg/m^2)] Group 3: 100 * [Cumulative dose (mg/m^2) / (960 ×	100 * [Cumulative dose (mg/m^2) / (2000 × number of cycles (mg/m^2)]	100 * [Cumulative dose (AUC) / (4 × number of cycles (AUC)]

Parameter	Trilaciclib	Gemcitabine	Carboplatin
	number of cycles (mg/m^2)]		

AUC = area under curve; BSA = body surface area; IV = intravenous.

5.2.1.4. Modifications of Study Therapy, Including Cycle (Dose) Delay, Skipped Doses, Dose Interruptions, and Dose Reductions.

- After Cycle 1, patients need to meet pre-specified laboratory parameter criteria before initiating Cycle 2 and each subsequent cycle of chemotherapy. A "Cycle Day Status" page asking if the patient was eligible to start a new cycle at the next visit is available on Days 15, 22, 29 and 36. If the patient is unable to start a new cycle at that next visit, then the cycle is delayed (the site answers "no"), the reason entered, and the question is asked again at the next visit until the patient either starts a new cycle or discontinues treatment. For example, if a patient returns to clinic on Day 22 and is unable to start a new cycle, the site answers the Cycle Day Status page on Day 15 as "no", enters the reason, and the patient returns to clinic on Day 29 for reassessment. The reasons for delay will be summarized as the first reason collected for a cycle in the following categories: (1) Hematological toxicity, (2) Non-hematological toxicity, (3) Other. In this particular setting, the term "hematological toxicity" is used to delineate those situations where the ANC and/or platelet values were lower than the per protocol requirements. It does not include settings where the patient had some other hematologic abnormality that could have led to a dose delay per the investigator's discretion.

- To receive Day 8/9 dose of each cycle, patients need to meet pre-specified laboratory parameter criteria. If the criteria is not met, the Day 8/9 doses are skipped. This information is collected "Cycle Day Status" page at Day 8/9. For "Did the patient receive chemotherapy at this visit?" if the answer is "no" then a skipped dose is counted. Similar to Day 1/2, the ANC must be $\geq 1.0 \times 10^9$/L in order to dose. The platelet count must be $\geq 75 \times 10^9$/L (vs. $\geq 75 \times 10^9$/L at Day 1/2). The reasons for skipped dose will be the same as the reasons for delay above. If a patient skips a dose on Day 8/9, and is able to receive dose at Day 15, then a new cycle will be started then. Otherwise that cycle will be counted as both a skipped dose and a delayed dose.

- Dose (mg/m^2) reductions are not permitted for trilaciclib. Dose reductions for carboplatin and gemcitabine are determined by comparing the planned dose on the respective drug administration pages between the current cycle and the previous cycle, and occur in the following order:
    - 1st Reduction: Carboplatin dose reduced from AUC 2 to AUC 1.5
    - 2nd Reduction: Gemcitabine dose reduced from 1000 to 800 mg/m^2.
    - 3rd Reduction: Discontinuation of either Carboplatin or Gemcitabine

  After the 3rd dose reduction, no further reductions are allowed, and patient will be discontinued. Dose reduction will happen only once per cycle and patients who have the dose reductions in a cycle will have the reduced dose administered for the rest of the cycle.

- Dose interruptions for all drugs are also captured on the dosing page and will be summarized for each study drug.

5.2.2. Adverse Events (AEs)

All AEs will be coded from verbatim text to PTs and grouped by SOC using the MedDRA Version 20.1. AEs will be collected from the time of signature of informed consent throughout the treatment period and up to 30 days after the last dose of study treatment. AEs are graded by investigator according to CTCAE, Version 4.03.

Any AE that started on or after the first dose of study drugs and up to the last dose + 30 days will be included as a treatment emergent AE (TEAE). AEs with an unknown/not reported onset date will also be included.

Other AE variables include drug-related AEs, AEs leading to study drug discontinuation or study withdrawal, AEs leading to death, and SAEs.

AEs with onset/end dates that are partially/completely missing will be imputed as follows:

(i) For onset date:
- If only the day part of the AE onset date is missing and occurs in the same month and year as the first dose date of study drug, the date of first dose of study drug will be used as the onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE;
- If the day and month parts of the AE onset date are missing and occur in the same year as the first dose of study drug, the date of the first dose of study drug will be used as the onset date of the AE. Otherwise, January 1st will be used to complete the onset date of the AE;
- If the AE onset date is completely missing, the date of the first dose of study drug will be used as the onset date of the AE.

(ii) For end date:
- If only the day part of the AE end date is missing, the last day of the month will be used to complete the end date of the AE;
- If the day and month parts of the AE end date are missing, December 31st will be used to complete the end date of the AE;
- If the AE end date is completely missing and the onset date of the AE occurs after the date of the first dose of study drug, the last date during the treatment period +30 days will be used as the AE end date. If the AE end date is completely missing and the onset date of the AE occurs prior to the date of the first dose of study drug the date of the first dose of study drug will be used as the AE end date.

AEs related to hematologic toxicity will be pooled based on the preferred MedDRA Version 20.1. Table 13 outlines those terms that will be consolidated.

Table 13 Preferred Terms to Be Consolidated

Presented term in the table	Preferred Term
Neutropenia	Neutropenia
	Neutrophil count decreased
Febrile neutropenia	Febrile neutropenia
Anaemia	Anaemia
	Anaemia macrocytic

Presented term in the table	Preferred Term
	Red blood cell count decreased
	Hemoglobin decreased
Thrombocytopenia	Thrombocytopenia
	Platelet count decreased
Lymphopenia	Lymphopenia
	Lymphocyte count decreased
Leukopenia	Leukopenia
	White blood cell count decreased

Infusion reaction AEs are signified in the study drug administration forms and that information is linked to the details entered on the AE page to distinguish those for a subset summary. Additionally, a summary from the AE data only will be presented for those records where "INFUSION RELATED REACTION" is a preferred term. The event terms are coded using the MedDRA Version 20.1.

5.2.3. Vital Signs

Vital signs include pulse rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height (only measured at screening), and body temperature. Body Mass Index (BMI) will be computed as weight (kg)/[height (m)]^2, Body Surface Area (BSA) will be computed using DuBois-DuBois formula as $0.20247 \times [\text{height (m)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$.

For vital signs, change from baseline to each post-baseline visit and timepoint will be calculated. Vitals will be summarized by visit as collected and not windowed.

The potentially clinically significant findings of vital signs will also be defined based on criteria defined in Table 14:

Table 14 Potentially Clinically Significant Criteria for Vital Signs

Vital Sign Parameter	Criterion value	Change from baseline
SBP	≥180 mmHg	Increase ≥40 mmHg
	≤ 90 mmHg	Decrease ≥40 mmHg
DBP	≥105 mmHg	Increase ≥20 mmHg
	≤ 50 mmHg	Decrease ≥20 mmHg
Pulse	≥ 120 bpm	Increase ≥40 bpm
	≤ 50 bpm	Decrease ≥40 bpm
Weight	n/a	Change ≥10%

bpm = beats per minute

5.2.4. Laboratory

Blood and urine samples for the determination of clinical chemistry, hematology, and urinalysis laboratory variables described in Table 15 will be measured.

Table 15 Laboratory Assessment

Lab Category	Lab tests
Hematology	hemoglobin, hematocrit, white blood cell (WBC), platelet counts, ANC, ALC, Monocyte Absolute, Basophil Absolute, Eosinophil Absolute, and other non-protocol specified tests
Chemistry	albumin, Alkaline Phosphatase (ALP), total bilirubin, calcium, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Lactate Dehydrogenase (LDH), sodium, and Blood Urea Nitrogen (BUN), and other non-protocol specified tests
Urinalysis	semiquantitative dipstick: specific gravity, pH, evaluation of glucose, protein, bilirubin, ketones, leukocytes, and hemoglobin microscopic examination, including RBC, WBC, and casts will be performed, if necessary

Change from baseline in laboratory test results to each assessment will be calculated; for hematology parameters, the change from cycle baseline will also be obtained. The urinalysis results will not be summarized; they will only be included in listings.

Clinical laboratory results will be graded according to CTCAE criteria, Version 4.03 which can be found in Table A-1 of Appendix. Any graded abnormality that occurs following the initiation of study drug and represents at least a 1-grade increase from the baseline assessment is defined as treatment emergent. Any assessment for which CTCAE toxicity grades are not available, will not be included in any analyses for which toxicity grades are required.

Analysis of Abnormal Hepatic Laboratory Values

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- ALT and/or AST >3x ULN, ALP < 2xULN, and Total Bilirubin> 2x ULN
- AST > 3,5,8,10, and 20x ULN, AST>5x ULN for more than 5 weeks
- ALT > 3,5,8,10, and 20x ULN, ALT > 5x ULN for more than 5 weeks
- Total Bilirubin >1.5 or >2x ULN

5.2.5. Electrocardiograms

Electrocardiogram (ECG) parameters include heart rate, PR interval, RR interval, and QT, QTcB, QTcF and QRS intervals. Change from baseline to each post-baseline visit will be calculated and summarized by visit as collected and not windowed. Visits and timepoints only collected for PK subjects will be listed but not summarized.

Collected QTcB and QTcF will not be used, but will instead be derived from the QT and RR (converted from collected msec to sec) interval based on the following formulas:

$$QTcB = \frac{QT}{\sqrt{RR}}$$

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

If QT and/or RR is missing, the QTcB and QTcF will be left as missing.

Potentially clinically significant ECG findings will be identified using the criteria which are included in Table 16. ECG results are interpreted as clinically significant or not clinically significant.

Table 16 Potentially Clinically Significant Criteria for ECG

ECG Parameter	Criterion value
Heart Rate	>120 bpm
	<50 bpm
PR Interval	≥ 210ms
RR Interval	> 1200ms
	< 500ms
QRS Interval	≥ 120ms
	≤ 50ms
QT Interval	≥ 500ms
	≤ 300ms
QTcB, QTcF Intervals	≥ 500ms
	≥ 480ms
	≥ 450ms
	≤ 300ms
	Change from baseline ≥ 30 ms

ECG Parameter	Criterion value
	Change from baseline ≥ 60 ms

5.2.6. Physical Examination

Physical examination is conducted during screening, on Day 1 of each cycle, Day 22 (and subsequent visits if applicable) at each cycle, and at the post-treatment visit. Abnormal findings in PE were to be reported as AEs. These data will not be summarized, i.e. they will only be available in listings.

6. ANALYSIS METHODS

6.1. General Principles of Analysis

6.1.1. General Methodology

In general, all efficacy, safety and PK variables will be summarized using descriptive statistics and graphs as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean, standard deviation, minimum, median, and maximum). Categorical variables will be summarized in frequency tables (frequencies and percentages). For PK variables, the geometric mean and coefficient of variation (CV) will be used instead of the arithmetic mean and standard deviation, if appropriate. Time to event variables will be analyzed with Kaplan-Meier method and summarized with median, twenty-fifth and seventy-fifth percentiles, and 95% confidence intervals (CI), if applicable. Individual data will be presented in patient listings.

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention, i.e. ICH-E3, will be used for all tables and listings. Upon completion, all SAS® programs will be validated by an independent programmer within the staff of the third-party vendor doing the primary analysis. In addition, the programming needed to generate a subset of outputs will be validated by an independent validation vendor. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings.

All summary tables, listings, and figures (TLFs) will be presented by treatment groups as defined in Table 17.

Table 17 Treatment Display in TLFs

Treatment Group	Treatment Description in Data Display
1	Group 1 (GC Day 1 and 8)
2	Group 2 (GC + Trilaciclib Day 1 and 8)
3	Group 3 (GC + Trilaciclib Day 1/2 and 8/9)
Combined 2 and 3	Group 2 and Group 3

All statistical tests will be presented at a two-sided significance level of 95% unless otherwise specified. The primary comparison will be conducted between Group 3 (GC + Trilaciclib Day 1/2 and 8/9) and Group 1 (GC therapy alone). The two additional comparisons (i.e. GC + Trilaciclib Day 1 and 8 vs GC therapy only; Combined Trilaciclib + GC therapy vs GC therapy only) will be considered supportive of the primary analyses and will not be alpha protected. Where appropriate, model-based point estimates, together with their 95% CIs will be presented along with the two-sided p-values for the tests. P-value will be presented to 4 decimal places, if the p-value <0.0001, the value will be presented as "<0.0001".

For continuous data, the same number of decimal places as in the raw data will be presented when reporting mean, median, minimum and maximum; one more decimal place than in the raw data will be presented when reporting standard deviation and standard error (SE). The derived variables will be presented with 1 decimal place. Percentages will be reported with 1 decimal

point; if the count is 0, no percentage will be presented. Value of percentage less than 1% will be presented as "<1%." Value of percentage less than 100% but ≥ 99.5% will be presented as ">99%."

6.1.2. Handling of Missing Data

In general, the observed case (OC) data for a visit will consist of the actual observations recorded for the visit. If missing, the OC data will remain missing — no missing imputation will be performed. Safety analyses will be conducted on the OC data only. However, imputation of missing AE and concomitant medication onset and stop dates will be used to determine the status of each AE and the prior/concomitant status of each medication. Please refer to Section 5.2.2 for the method of imputation of missing AE onset and stop date and Section 6.2.5 for the method of imputation of missing concomitant onset and stop dates.

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. Patients with missing data will be excluded only from analyses for which data are not available.

6.1.3. Visit Windowing

It is expected that there will be a variation between patients in the actual number of study days from the start of administration of study drug within each cycle – defined as Day 1 – to the dates that the scheduled visits occur. To handle this, for tables and figures where data are grouped by visit, assessments will be categorized using visit windows based on study days (relative to the Day 1 of each cycle). The visit-window mapping is described in Table 18. Visit-based summaries will be based on the windowed visits. All data, whether or not within the visit windows, will be presented in patients listings.

For windowed visits during the treatment cycles, if more than 1 visit occurs during a visit window, the visit closest to the scheduled day will be assigned to the windowed visit. If two visits are equidistant from the scheduled day, the later visit will be assigned to the windowed visit. If there are multiple assessments on the same day, the worst case will be used. For the assigned follow-up visit, the last assessment in the window will be included in the summary.

Table 18 Visit Windowing

	Cycle 1/ Odd cycle (2X-1)				Cycle 2/ Even cycle (2X)				Post-treatment	Post-Treatment Visit + 60 days [e]
Visit	**C1D1**	**C1D8**	**C1D15**	**EOC1**	**C2D1**	**C2D8**	**C2D15**	**EOC2**		
Scheduled Day [a]	1	8	15	22	1	8	15	22		
Clinical Chemistry [b]	Day -3 to 1			2 to EOC	Day -3 to 1			2 to EOC	From first dose date of last cycle to first dose date of last cycle + 30	Relative to the first dose date of last cycle, the last assessment falling the window between 31 and 89.
Hematology [c] – cycles without skipped dose	Day -1 to 1	2 to 11	12 to 18	19 to EOC	Day -1 to 1	2 to 11	12 to 18	19 to EOC	From first dose date of last cycle to first dose date of last cycle + 30	Relative to the first dose date of last cycle, the last assessment falling the window between 31 and 89.
Hematology [c] – Cycles with skipped dose	Day -1 to 1	2 to 11	[d]	12 to EOC [d]	Day -1 to 1	2 to 11	[d]	12 to EOC [d]	From first dose date of last cycle to first dose date of last cycle + 30	Relative to the first dose date of last cycle, the last assessment falling the window between 31 and 89.

[a] The scheduled day is relative to the Day 1 of each cycle.
[b] Clinical chemistry may be obtained up to 72 hours prior to the first dose of each cycle.
[c] Hematology may be obtained up to 24 hours prior to dosing on Days 1 and 8 of each cycle, Day 15 of each cycle, at the Post-Treatment Visit, and at 60 days after the Post-Treatment Visit.
[d] For cycles where the Day 8/9 dose is skipped, there will not be a Day 15 visit, only End of Cycle
[e] 60 ± 7 days after the post-treatment visit only for hematologic parameters and CCI [redacted].
Note: Since (1) the end date of a cycle (EOC) is defined as the date of Day 1 study drug administration of the next cycle and (2) toxicity can alter the timing of Day 1, the actual day for EOC may vary. For the last cycle (where no subsequent cycle is given), the end of cycle will be defined as Day 22 relative to the first dose of the cycle with a +7 days visit window. Hence, for the last cycle, the window for EOC is 22-30.

6.1.4. Adjustment for Covariates

Prior to Protocol Amendment 3 Version 4.0, patient randomization was stratified by liver involvement (yes or no) and Eastern Cooperative Oncology Group (ECOG) status (0 or 1). With implementation of Amendment 3, the stratification factors were changed to number of prior lines of systemic therapy (0 vs. 1 or 2) and liver involvement. The number of prior lines of systemic therapy was retrospectively collected for those patients randomized prior to the Amendment 3. The efficacy analyses will use liver involvement and number of prior lines of therapy as covariates in statistical models. Where necessary, additional sensitivity analyses will be performed with liver involvement and ECOG status as covariates instead. Where not collected on the randomization page, values will be derived from other eCRF pages.

6.2. Analysis Methods

6.2.1. Patient Disposition

A summary table will be generated to provide the following by study part, as appropriate:

- Number of patients screened
- Number and percentage of screening failures
- Reason for screening failure
- Number of patients dosed
- Number of patients randomized
- Number of patients randomized and not dosed

A separate table will be presented to show the patients included in each analysis set and reason for exclusion from an analysis set.

Patient status at treatment and study completion will be listed and summarized. The listing will include whether patients discontinued from the treatment and the reasons for the discontinuation, along with the date of first and last dose and the date of completion or discontinuation from the treatment. The same information will be provided for patients who discontinued from the study. The following summaries will be added to the disposition table:

- End of treatment status (discontinued/ongoing for each study drug)
- Reason for study drug discontinuation (for each study drug)
- Number of patients going into Survival follow-up
- Number and percentage of patients who discontinued the study
- Reason for study discontinuation
- Death and reason for death

6.2.2. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics, such as age at informed consent date, age groups (18-65, >65-75, >75), gender, race, ethnicity, country, screening vital signs (body weight, height, BMI, BSA), ECOG status, prior lines of therapy, liver involvement, and smoking history (never smoker, former smoker and current smoker), will be summarized and listed.

6.2.3. Disease Characteristics

Disease characteristics including breast cancer gene (BRCA) classification, histological classification of initial breast cancer diagnosis, stage of initial breast cancer diagnosis, stage of TNBC diagnosis, stage at time of enrollment, and brain scan results will be summarized and listed. Date of initial breast cancer diagnosis, and date of TNBC diagnosis will be listed only.

6.2.4. Medical/Surgical History

Medical history will be coded to SOC and PT using MedDRA Version 20.1.

The number and percentage of randomized patients with any past medical/surgical history within each SOC and PT will be provided. A patient will only be counted once within a particular SOC (PT) even if he/she has multiple conditions/diseases in the same SOC (PT). The conditions/diseases from medical history are those conditions/diseases that stopped prior to the study entry. Additionally, breast cancer surgeries will be summarized separately.

6.2.5. Concomitant Medications

All medication verbatim terms collected will be coded to Anatomical Therapeutic Classification (ATC) and PT using the WHO-DD Version Sep2017.

Prior medications are defined as those taken by the patient prior to the administration of study drug. Concomitant medications are defined as those taken by the patient at any time between the date of study drug administration and study completion/discontinuation. Medication with start date/time being partially or completely missing will be assumed to be concomitant if it cannot be definitely shown that the medication did not occur during the treatment period.

Medications with onset/end dates that are partially/completely missing will be imputed as follows:

(i) For onset date:
- If only the day part of the medication onset date is missing and occurs in the same month and year as the first dose date of study drug, the date of first dose of study drug will be used as the onset date of the medication. Otherwise, the first day of the month will be used to complete the onset date of the medication;
- If the day and month parts of medication onset date are missing and occur in the same year as the first dose of study drug, the date of the first dose of study drug will be used as the onset date of the medication. Otherwise, January 1st will be used to complete the onset date of the medication;
- If the medication onset date is completely missing, the date of the first dose of study drug will be used as the onset date of the medication.

(ii) For end date:
- If only the day part of the medication end date is missing, the last day of the month will be used to complete the end date of the medication;
- If the day and month parts of the medication end date are missing, December 31st will be used to complete the onset date of the medication;
- If the medication end date is completely missing and the onset date of the medication occurs after the date of the first dose of study drug, the last date during the treatment period will be

used as the medication end date. Otherwise, the date of the first dose of study drug will be used as the medication end date.

Concomitant medications will be summarized by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class.

All prior and concomitant medications will be presented in a patient listing.

6.2.6. Prior and Subsequent Anti-Cancer Therapy

The prior anti-cancer therapies, such as prior systemic anti-cancer therapy (Yes or No), prior breast cancer surgery (Yes or No), and prior radiotherapy (Yes or No), will be summarized and listed. All verbatim terms collected of prior and subsequent anti-cancer therapy will be coded to Anatomical Therapeutic Classification (ATC) and PT using the WHO-DD Version Sep2017.

The prior and subsequent anti-cancer therapy will be summarized separately by presenting the number and percentage of patients by PT and ATC. Patients taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class. The data will be presented in a patient listing.

For subsequent anti-cancer therapy, if the term contains the word “RADIATION” or ‘RADIOTHERAPY’, the therapy will be classified to radiotherapy; it is classified as systemic anti-cancer therapy unless the therapy can be grouped to surgery. The number and percentage of randomized patients receiving subsequent anti-cancer therapy will be provided by systemic anti-cancer therapy (by drug name and by line), radiotherapy, and surgery. All subsequent anti-cancer therapies will be presented in a patient listing.

6.2.7. Efficacy Analyses

All the efficacy variables will be summarized using descriptive statistics by cycle or visit, with the supportive data provided in patient listings. Data will be summarized using descriptive statistics and the between treatment comparison (trilaciclib days 1/2/8/9, trilaciclib days 1/8, and combined trilaciclib vs GC only), will be performed only for the primary and secondary endpoints outlined in Sections 5.1.1 – 5.1.3. The primary comparisons will be between trilaciclib days 1/2/8/9 vs. GC only and will be built into the multiplicity adjustment described in Section 6.2.7.1.4. Though relevant statistical tests will be conducted for other treatment comparisons, the information to be presented will be considered to be supportive. For these comparisons, all statistical tests will be conducted at a two-sided significance level of 5% unless otherwise specified. Where appropriate, model-based point estimates, together with their two-sided 95% CIs will be presented along with the two-sided p-value for the test unless otherwise specified. Graphical presentation of efficacy results will be performed as needed.

Unless otherwise specified, all analyses for the efficacy endpoints will be conducted for the treatment period which is defined to be between the date of randomization and the end of the last cycle.

6.2.7.1 Primary and Key Secondary Efficacy Analyses

6.2.7.1.1 Primary Efficacy Analyses

The primary efficacy endpoint, occurrence of SVN, is a binary response variable (Yes, No). It will be summarized using descriptive statistics by treatment group and will be analyzed to compare trilaciclib and GC only using modified Poisson regression (Zou, 2004) to account for the variable duration of the treatment period for each patient. The model will include baseline ANC as a covariate, the stratification factors of prior lines of systemic therapy (0 vs. 1 or 2) and liver involvement (Yes vs No), and treatment as a fixed effect. The logarithm transformation of number of cycles will be included as an offset variable in the modeling. The two-sided p-value, adjusted rate ratio (aRR) (trilaciclib vs GC only) and its 95% CIs will be presented.

For the other primary efficacy endpoint, DSN in Cycle 1 based on Strategy 1 in Section 5.1.1.2.1, a two-sided p-value will be calculated for the nonparametric analysis of covariance (ANCOVA) (Stokes 2012). The nonparametric ANCOVA will include study baseline ANC value as covariate, stratification factors of lines of systemic therapy (0 vs. 1 or 2) and liver involvement (Yes vs No), and treatment as a fixed effect. Along with the descriptive statistics, the mean difference and Hodges-Lehmann estimate of median difference between the two treatment groups, together with its 95% CIs will be provided. Additionally, DSN for each cycle will be presented using descriptive statistics.

6.2.7.1.2 Key Secondary Efficacy Analyses

Occurrence of RBC transfusions on/after 5 weeks on study is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1 except baseline HGB will be used as a covariate instead of baseline ANC in the modified Poisson model. Also, the offset will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles, and. An additional sensitivity analysis will look all transfusions during the treatment period, and all transfusions with a subset of subjects completing at least 1 cycle.

Occurrence of GCSF administration is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1.

Occurrence of all-cause dose reductions is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1.

Occurrence of platelet transfusion is a binary variable and will be summarized using the same method for occurrence of SVN described in Section 6.2.7.1.1 except baseline platelet count will be used as a covariate instead of baseline ANC in the modified Poisson model. Also, the offset will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles.

6.2.7.1.3 Key Secondary OS Analyses

OS will be summarized using Kaplan-Meier method, and the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs will be calculated. It will be based on the ITT analysis set. The supportive data listings will also be provided.

In addition to the quartile summary from Kaplan-Meier method, Kaplan-Meier estimates will be provided for the survival rates at 3, 6, 9, and 12 months along with their 95% CIs.

Additionally, a comparison will be conducted between trilaciclib and GC only. The two-sided p-value from a Cox proportional hazard model will be presented, the model includes treatment and stratification factors as fixed effects. The HR between the two treatment groups, together with its 95% CIs will be presented.

6.2.7.1.4 Multiplicity Adjustments

The clinical trial evaluates the objectives defined in terms of the comparison of Group 3 (GC + Trilaciclib Day 1/2 and 8/9) to Group 1 (GC therapy alone) on the primary and key secondary myelosuppression efficacy endpoints in Sections 5.1.1 and 5.1.2. The resulting multiplicity problem include the following six hypotheses of no effect:

- Hypothesis H_1. Comparison of Group 3 versus Group 1 for duration of severe (Grade 4) neutropenia in Cycle 1.
- Hypothesis H_2. Comparison of Group 3 versus Group 1 for occurrence of severe (Grade 4) neutropenia.
- Hypothesis H_3. Comparison of Group 3 versus Group 1 for all-cause dose reductions in the MAHE composite.
- Hypothesis H_4. Comparison of Group 3 versus Group 1 for occurrence of RBC transfusions on/after Week 5 on study.
- Hypothesis H_5. Comparison of Group 3 versus Group 1 for occurrence of G-CSF administration.
- Hypothesis H_6. Comparison of Group 3 versus Group 1 for occurrence of platelet transfusions.

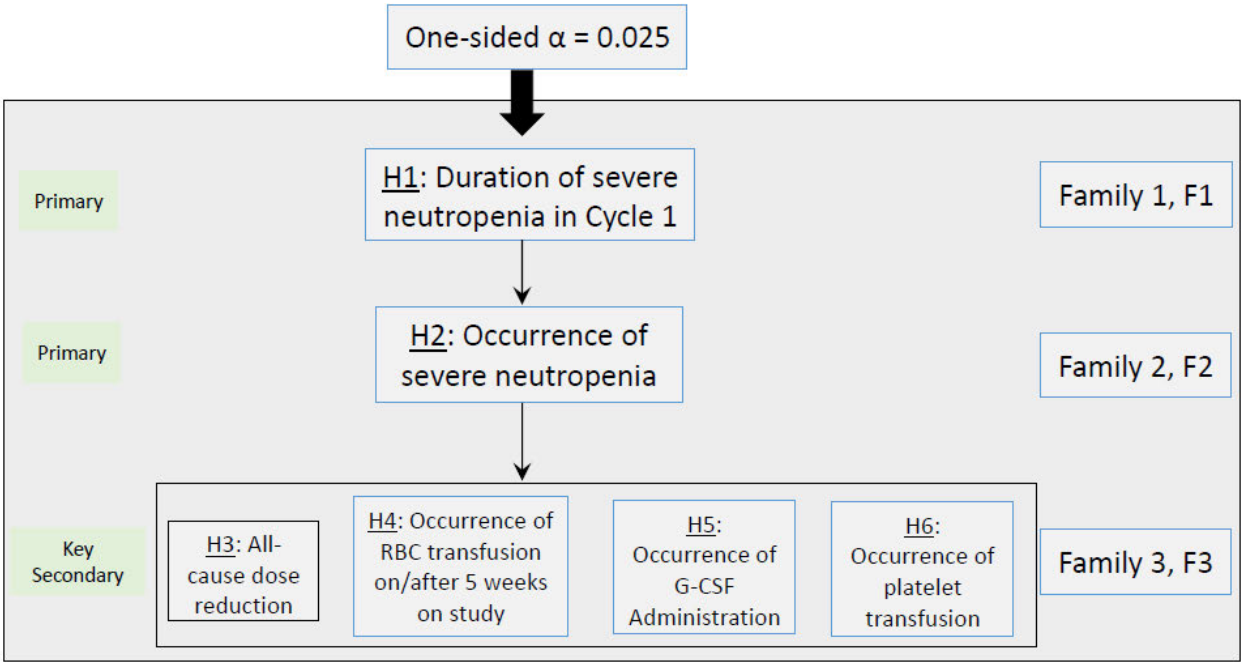
A Hochberg-based gatekeeping procedure will be utilized to control the global familywise error rate across the multiple null hypotheses in the strong sense at a 1-sided α=0.025 level. The one-sided p-values for these comparisons will be used for the multiple test procedure, and the raw and adjusted 1-sided p-values will be provided in the summary.

Gatekeeping procedure with logical restrictions

A Hochberg-based gatekeeping procedure satisfies the positive dependence condition given the 1-sided setting. The procedure is built using the mixture methodology developed in Dmitrienko and Tamhane (2011) and accounts for the logical restrictions among the six hypotheses displayed in Figure 1 by performing multiplicity adjustments in three steps. The logical restrictions can be achieved by defining the parallel set and serial set for each individual hypothesis based the tree-structured procedure introduced by Dmitrienko et al (2007).

- Step 1. The Group 3 versus Group 1 comparisons for Family 1 (hypothesis H_1) is performed using a truncated version of the Hochberg procedure. The truncation parameter γ is set to 0.
- Step 2. The Group 3 versus Group 1 comparisons for Family 2 (hypothesis H_2) is performed using a truncated version of the Hochberg procedure if H_1 is significant in Step 1. The truncation parameter γ is set to 0.
- Step 3. The Group 3 versus Group 1 comparisons for Family 3 (hypotheses H_3, H_4, H_5, and H_6) are performed using the regular Hochberg test if H_2 is significant in Step 2.

Figure 1 Graphical Display of the Hochberg-based Gatekeeping Procedure



The logical restrictions in the Step 1 and Step 2 contain only one single hypothesis, and the Step 3 has three hypotheses H_3, H_4, H_5, though the testing procedure can be broadly considered as a fixed sequence procedure, its implementation can be performed through the framework of Hochberg-based gatekeeping procedure as described in detail below.

The regular Hochberg test is defined in Dmitrienko et al. (2009) and the truncated Hochberg test is defined in Dmitrienko, Tamhane and Wiens (2008). The decision rules used in the regular and truncated Hochberg tests will be detailed in the following. In general terms, the truncated version of the Hochberg test is defined as a convex combination of the regular Hochberg and Bonferroni tests. An important parameter of the truncated Hochberg test is the truncation parameter γ which ranges between 0 and 1. If the truncation parameter γ is set to 0, the truncated Hochberg test simplifies to the Bonferroni test. On the other hand, if the truncation parameter γ is set to 1, the truncated Hochberg test is identical to the regular Hochberg test. The truncated Hochberg test satisfies the separability condition (Dmitrienko, Tamhane and Wiens, 2008) if the truncation parameter γ is strictly less than 1. This condition ensures that in each step of the testing algorithm the error rate can be transferred to the next step provided at least one Group 3 versus Group 1 comparison is significant in the current step without inflating the overall type I error rate (Huque, 2016; FDA, 2017).

Testing algorithm

This section describes the implementation of the Hochberg-based gatekeeping procedure. The testing algorithm relies on the general approach to defining multistage gatekeeping procedures based on mixtures of multiple tests proposed in Dmitrienko and Tamhane (2011).

Decision rules

The aforementioned 6 hypotheses are grouped into 3 families:

- Family 1 (F_1) includes the hypotheses H_1.
- Family 2 (F_2) includes the hypothesis H_2.
- Family 3 (F_3) includes the hypotheses H_3, H_4, H_5, and H_6.

Using more compact notation, the families are defined as follows:

$$F_1 = \{H_i, i \in N_1\},\ F_2 = \{H_i, i \in N_2\},\ F_3 = \{H_i, i \in N_3\}.$$

where the index sets are defined as $N_1 = \{1\},\ N_2 = \{2\},\ N_3 = \{3, 4, 5, 6\}$. Let t_i and p_i denote the test statistic and 1-sided p-values associated with the hypotheses, respectively. Let α denote the global familywise error rate, i.e., one-sided $\alpha = 0.025$.

Consider the closed family associated with Families 1, 2 and 3, i.e., a family of all non-empty intersections of the twelve hypotheses. Each intersection will be identified by an index set

$$I \subseteq N\ =\ \{1,\ldots,6\}$$

(note that the empty set is excluded). For example, the index vector $I = \{1, 2, 5\}$ corresponds to the intersection of the hypotheses H_1, H_2, and H_5.

To construct the Hochberg-based gatekeeping procedure that controls the global familywise error rate in the strong sense at an α level, an α-level test needs to be defined for each intersection in the closed family. The multiple test and associated p-value for an intersection are computed in two steps.

Step 1: Define p-values for subset intersections

Consider an intersection corresponding to the index set $I \subseteq N$ and define the index sets $I_k = I \cap N_k$, $k = 1, 2, 3$. The p-values for the index sets I_1, I_2, and I_3 are computed as follows:

Let n_1 denote the number of hypotheses included in I_1 and let $m_1 = n_1$. If $n_1 > 0$, the truncated Hochbergp-value is defined using the ordered p-values associated with the hypotheses included in the index set I_1, denoted by

$$p_{1(1)} \leq \cdots \leq p_{1(m_1)}$$

The truncated Hochberg p-value for the index set I_1 is given by

$$p(I_1) = \min_{i=1,\cdots,m_1} \frac{p_{1(i)}}{\frac{\gamma_1}{m_1 - i + 1} + (1 - \gamma_1)}$$

Here γ_1 is the pre-specified truncation parameter in Family 1. Choosing a larger value of γ_1 improves the power of comparisons in Family 1, and γ_1 is set to 0.

Further, let n_2 denote the number of hypotheses included in the index set I_2. If $n_2 > 0$, consider the hypotheses in the index set I_2 and remove the hypotheses that are not consistent with the logical restrictions defined in Figure 1. Let m_2 denote the number of hypotheses remaining in the index set I_2 after this logical restriction operation. If $m_2 > 0$, let

$$p_{2(1)} \leq \cdots \leq p_{2(m_2)}$$

denote the ordered p-values for the hypotheses remaining in the index set I_2. The truncated Hochberg p-value for I_2 is given by

$$p(I_2) = \min_{i=1,\cdots,m_2} \frac{p_{2(i)}}{\frac{\gamma_2}{m_2 - i + 1} + (1 - \gamma_1)}$$

where γ_2 is the pre-specified truncation parameter in Family 2, which plays the same role as γ_1 in Family 1, and γ_2 is set to 0.

Finally, let n_3 denote the number of hypotheses included in I_3. If $n_3 > 0$, remove the hypotheses that are not consistent with the logical restrictions defined in Figure 1. Let m_3 denote the number of hypotheses remaining in the index set I_3 after this logical restriction operation. If $m_3 > 0$, let

$$p_{3(1)} \leq \cdots \leq p_{3(m_3)}$$

denote the ordered p-values for the hypotheses remaining in the index set I_3. The Hochberg p-value for I_3 is given by

$$p(I_3) = \min_{i=1,\cdots,m_3} \frac{p_{3(i)}}{\frac{1}{m_3 - i + 1}}$$

Step 2: Define overall *p*-value

The overall p-value for the intersection corresponding to the index set I is computed by combining the p-values associated with the index sets I_1, I_2, and I_3. Consider the following three scenarios:

- If $n_1 > 0$, the overall p-value is found using the following mixing function:

$$p(I) = \min\left(\frac{p(I_1)}{b_1}, \frac{p(I_2)}{b_2}, \frac{p(I_3)}{b_3}\right)$$

where $b_1 = 1,\ b_2 = b_1(1 - f_1),\ b_3 = b_2(1 - f_2)$ and f_1 and f_2 are computed based on the error rate functions of the truncated Hochberg tests used in Families 1 and 2. These quantities are defined below.

- If $n_1 = 0$ and $n_2 > 0$, the overall p-value is given by

$$p(I) = \min\left(\frac{p(I_2)}{b_2}, \frac{p(I_3)}{b_3}\right)$$

where $b_2 = 1,\ b_3 = b_2(1 - f_2)$.

- If $n_1 = 0, n_2 = 0$ and $n_3 > 0$, the overall p-value is given by

$$p(I) = \frac{p(I_3)}{b_3}$$

where $b_3 = 1$.

The error rate function of the truncated Hochberg test with the truncation parameter γ_k for testing an intersection corresponding to the index set I_k, $k = 1, 2$, is defined as

$$e_k(I_k) = P[p(I_k) \leq \alpha]$$

and $f_k = e_k(I_k)/\alpha$, $k = 1, 2$. It is shown in Brechenmacher et al. (2011) that

$$e_k(I_k) = [\gamma_k + (1 - \gamma_k)|I_k|/n_k]\alpha$$

if the index set I_k is non-empty and $e_k(I_k) = 0$ the index set I_k is empty. Here $|I_k|$ denotes the number of hypotheses included in the index set I_k.

As shown in Dmitrienko and Tamhane (2011), the resulting test for the intersection corresponding to the index set I is an α-level test. This implies that the Hochberg-based gatekeeping procedure controls the global familywise error rate in the strong sense at a one-sided $\alpha = 0.025$.

Multiplicity-adjusted p-values

Multiplicity-adjusted p-values for the Hochberg-based gatekeeping procedure are computed using the closure principle. For each hypothesis, the adjusted p-value is defined as the maximum over the p-values associated with the intersections in the closed family that include the hypothesis of interest. For example, the adjusted p-value for H_2 is the maximum over the p-values for intersections containing H_2. The calculations are performed using the decision matrix algorithm, see Dmitrienko and Tamhane (2011).

Regular and truncated Hochberg tests

Consider a general problem of testing m null hypotheses denoted by $H_1, \ldots, H_m$. Let $p_1, \ldots, p_m$ denote the associated raw p-values. Further, let $p_{(1)} < \cdots < p_{(m)}$ denote the ordered p-values and $H_{(1)} < \cdots < H_{(m)}$ denote the hypotheses corresponding to the ordered p-values.

The regular Hochberg test is based on the following testing algorithm:

- Step 1: If $p_{(m)} > \alpha$, accept $H_{(m)}$ and go to Step 2, otherwise reject all null hypotheses and stop.
- Step $i = 2, \ldots, m-1$: If $p_{(m-i+1)} > \alpha/i$, accept $H_{(m-i+1)}$ and go to Step $i+1$, otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$, otherwise reject $H_{(1)}$.

The truncated Hochberg test with the truncation parameter γ is based on the following testing algorithm:

- Step 1: If $p_{(m)} > [\gamma + (1-\gamma)/m]\alpha$, accept $H_{(m)}$ and go to Step 2, otherwise reject all null hypotheses and stop.
- Step $i = 2, \ldots, m-1$: If $p_{(m-i+1)} > [\gamma/i + (1-\gamma)/m]\alpha$, accept $H_{(m-i+1)}$ and go to Step $i+1$, otherwise reject all remaining null hypotheses and stop.
- Step m: If $p_{(1)} > \alpha/m$, accept $H_{(1)}$, otherwise reject $H_{(1)}$

6.2.7.1.5 Robustness of Primary and Key Secondary Efficacy Analyses

A binary response variable (Yes, No) will be analyzed to compare trilaciclib and GC only using stratum-adjusted method to account for the liver involvement (Yes or No) and number of prior lines of therapy (0, 1-2) as the stratification factor. The adjusted proportion difference (trilaciclib vs GC only) and its 95% CIs will be calculated using Cochran-Mantel-Haenszel (CMH) weight outlined in Kim et al. 2013. The two-sided p-value will be calculated using stratified exact CMH

method. Additionally, three sets of sensitivity analysis will be conducted to evaluate the robustness of the results from primary or key secondary analyses for a binary response variable (Yes, No).

(i) For patients who die during the treatment period without experiencing an event, Yes will be assigned to the variable.

(ii) After the imputation from (i), a worst-comparison analysis will be done to establish a stringent boundary of the treatment effect. Patients who die during the treatment period will still be set to Yes, and patients who discontinue the study prior to the July 30, 2018 data cutoff date without experiencing an event will then be imputed. If the patient is from the GC only group, No will be assigned to the variables, Yes will be assigned to the trilaciclib groups.

(iii) After the imputation from (i), a tipping-point analysis (Yan et al,. 2009) will be performed by assigning the response to the variable for patients who discontinue the study early during the treatment period without experiencing an event.

The tipping-point analysis assumes all possible combinations of numbers of Yes and No for the missing responses (defined as patients without an event who have discontinued the study prior to the July 30, 2018 data cutoff date) in the trilaciclib and GC only groups. For example, let n_t be the number of randomized trilaciclib patients with missing response and n_c be the number of randomized GC only patients with missing responses. For the trilaciclib patients with missing values, there are $n_t + 1$ possible assumptions for number of No (i.e. 0, 1, 2, …, to n_t); for the GC only patients with missing values, there are $n_c + 1$ possible assumptions for number of No. Therefore, there are total of $(n_t + 1) \times (n_c + 1)$ possible combination of assumptions for number of No and Yes for the trilaciclib and GC only patients with missing responses. The un-stratified exact CMH method will be performed on the available responses with each of these $(n_t + 1) \times (n_c + 1)$ assumptions and will be summarized. A figure will be presented with points representing each possible combination where the significant p-value 'tips' to greater than a one-sided 0.025, which would represent a change in the study conclusions. Clinical justification will be provided to evaluate whether the assumption is plausible.

Each of the analyses will be repeated using two additional distinct data sets to evaluate the confounding effect of GCSF administration: inclusion of only those patients or cycles who had concurrent GCSF administration; and inclusion of only those patients or cycles who did NOT have concurrent GCSF administration. The "with" and "without" GCSF analyses are subsets of the total number of patients or cycles.

Each of the analyses will be similarly repeated for subsets of cycles with and without skipped doses.

DSN, Strategy 2 (refer to Section 5.1.1.2.2) endpoint will be summarized using Kaplan-Meier method, and the descriptive statistics of median, 25% and 75% percentiles along with their 95% CIs will be calculated for. Additionally, DSN for each cycle will be presented using descriptive statistics.

In addition to the summary from Kaplan-Meier method, the two-sided p-value will be obtained from the stratified Kaplan-Meier method to account for the stratification factors. The hazard ratio (HR) between the two treatments (trilaciclib vs GC only), together with its 95% CIs will be

calculated from a Cox proportional hazard model in which treatment and the stratification factors will be included as fixed effects.

The primary and key secondary efficacy endpoints are based on the ITT analysis set, and the analysis will be repeated for the mITT analysis set and PP analysis set.

6.2.7.2 Supportive Secondary Efficacy Analyses

6.2.7.2.1 Analysis of Total Number of MAHE

The total number of MAHE in Section 5.1.2.15.1.3.1 will be analyzed to compare trilaciclib and GC only using a negative binomial regression model to account for the potential over-dispersion. The model includes the stratification factors of prior lines of systemic therapy (0 vs. 1 or 2) and liver involvement (Yes vs No), and treatment as a fixed effect. The logarithm transformation of duration of treatment period divided by 7 (i.e. week) will be included as an offset variable in the modeling. The two -sided p-value, aRR (trilaciclib vs GC only) and its 95% CIs will be presented.

The total number of MAHE will be summarized descriptively, along with the weeks of duration, and the event rate per week (calculated as the total number of events/ duration of treatment period divided by 7 [i.e. week]). The cumulative incidence of events during the treatment period will be summarized and presented graphically in three-week intervals.

The total number of individual MAHE components (specified in Table 5) will be summarized similarly.

Time-to-first MAHE endpoints (overall and individually) in Section 5.1.3.1 will be summarized similar to DSN, Strategy 2 as described in Section 6.2.7.1.5. A graphical display of cumulative incidence will also be presented.

The MAHE endpoints are based on the ITT analysis set, and the analysis will be repeated for the mITT analysis set and PP analysis set.

6.2.7.2.2 Analyses of Objective Response

The patients in each category of TPR according to the investigator tumor assessment (CR, PR, SD, PD, or NE) will be presented in a data listing. The number and percentage of patients in each category of BOR (Confirmed CR, Confirmed PR, SD, PD, or NE), ORR, $ORR_{UNCONFIRMED}$ and CBR according to the investigator tumor assessment (Confirmed CR, Confirmed PR, SD, PD, or NE) will be summarized. Detailed information of deriving tumor relevant responses is provided in Section 5.1.3.2.4.

Similar analyses will be repeated based on the derived responses according to the RECIST Version 1.1.

Estimates of response rate, along with its associated exact 95% two-sided CIs using Clopper-Pearson method will be computed for ORR and CBR within each treatment group.

The binary endpoint (Yes, No) of ORR for the two treatments (trilaciclib and GC only) will be analyzed to compare trilaciclib and GC only using stratum-adjusted method to account for the stratification factors. The adjusted proportion difference (trilaciclib vs GC only) and its 95% CIs will be calculated using CMH weight outlined in Kim et al. 2013. The two-sided p-value will be calculated using stratified exact CMH method.

The analyses are based on the response evaluable analysis set. The supportive data listings will also be provided.

6.2.7.2.3 Analyses of DOR and PFS

The analysis method as described in Section 6.2.7.1.36.2.7.1.5 for OS will be applied to PFS (derived, and derived with clinical progression) and DOR (investigator and derived), except DOR will exclude the Kaplan-Meier estimates for the survival rates at 3, 6, 9, and 12 months as well as the Cox proportional hazard model.

For DOR, the analysis is based on the response evaluable analysis set; for PFS the analysis will be based on the ITT. The supportive data listings will also be provided. For the PFS, the derived endpoint based on only radiologic progression will be considered as the primary, and the derived endpoint based on both radiologic and clinical progression will be considered as supportive.

6.2.7.2.4 Analyses of Hematology Lab Values

For the endpoints specified in Section 5.1.3.4 and 5.1.3.5, in addition to descriptive statistics summary, graphical displays will be provided to facilitate evaluation of trends in the change in a given variable over time. Moreover, each of the ANC change over time analysis (i.e. observed value at windowed visit and cycle nadir) specified above will be done using three distinct data sets to evaluate the confounding effect of GCSF administration: all patients or cycles regardless of GCSF administration; inclusion of only those patients or cycles who had concurrent GCSF administration; and inclusion of only those patients or cycles who did NOT have concurrent GCSF administration. The "with" and "without" GCSF analyses are subsets of the total number of patients or cycles.

6.2.7.2.5 Analyses of Other Binary Efficacy Endpoints

The following binary response variables (Yes, No) will be analyzed using the same method for occurrence of SVN except baseline ANC will not be a covariate in the modified Poisson model. See Section 6.2.7.1.1:

- Occurrence of a Grade 3 or 4 hematologic toxicity during the treatment period (refer to Section 5.1.3.3);
- Occurrence of an ESA administration during the treatment period (refer to Section 5.1.3.6);
- Occurrence of an IV antibiotic administration during the treatment period (refer to Section 5.1.3.7); The offset in the modified Poisson model will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles. Additionally, total number of IV antibiotic administrations will be summarized descriptively.
- Occurrence of an infection SAE during the treatment period (refer to Section 5.1.3.8); The offset in the modified Poisson model will be the logarithm transformation of duration of treatment period divided by 7 (i.e. week) instead of number of cycles. Additionally total number of infection SAEs will be summarized descriptively.
- Occurrence of a Grade 4 and Grade 3 or 4 thrombocytopenia during the treatment period (refer to Section 5.1.3.10);

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6.2.8. Safety Analyses

All safety analyses will be based on the safety analysis set, as defined in Section 3.1.3. Descriptive statistics will be used to summarize the safety outcomes. The continuous safety variables will be summarized at each visit including end of each cycle (the last non-missing assessment during the cycle), end of treatment (the last non-missing assessment during the treatment period), and end of study (the last non-missing assessment during the whole study), if applicable. No inferential analyses of safety data are planned unless otherwise specified.

6.2.8.1. Chemotherapy Exposure and Compliance Analyses

Duration on treatment and number of cycles will be summarized by treatment. For each study drug, the dosing endpoints described in Section 5.2.1 will be summarized by treatment.

Dose modifications will be summarized for each study drug (gemcitabine, carboplatin or trilaciclib) including the following:

- Number of cycles received;
- Number of skipped doses;
- Number of dose reductions;
- Number of dose interruptions;
- Number of patients with skipped doses;
- Number of patients with dose reductions;
- Number of patients with dose interruptions.

The number of cycles delayed, the number and percentage of patients experiencing a treatment cycle delay, and reason for cycle delay will be summarized by treatment. The study dosing records and the derived dosing endpoints will be listed.

6.2.8.2. Adverse Events

Number and incidence rates of AEs will be summarized by SOC and/or PT for the following categories of TEAEs: all AEs, SAEs, AEs leading to death, and AEs leading to study drug discontinuation or study withdrawal. Patients with more than one occurrence of the same SOC (PT) will be counted only once within the SOC (PT) categorization.

AEs will also be summarized similarly by CTCAE grade and relationship to any study drug (gemcitabine, carboplatin or trilaciclib), and by relationship to each drug. Should a patient experience more than one occurrence of the same SOC (PT), the patient's worst occurrence (worst grade/most related causality) will be retained in the tabulation.

All AEs, including AEs that started prior to the study medication, will be presented in patient listings. In addition, separate listings of all SAEs, AEs leading to death, drug-related AEs, and AEs leading to study drug discontinuation or study withdrawal will be provided.

The criteria for identifying infusion related reaction AEs or hematologic toxicity AEs are described in Section 5.2.2. A summary table showing the incidence of each category of AEs related to infusion and related to hematologic toxicity will be presented along with its supportive data listing.

6.2.8.3. Laboratory Evaluations

For hematology and clinical chemistry labs, the observed values and change from baseline will be summarized separately for cycles with and without a skipped dose for each visit during the treatment period using descriptive statistics.

Toxicities for clinical labs will be characterized according to CTCAE, Version 4.03 (Table A-1 of Appendix when possible), and the frequency and percentage of patients with each CTCAE grade for each visit (separately by cycles with and without a skipped dose) during the treatment period will be described. Moreover, any occurrence of grade 3 or grade 4 during the treatment period will be summarized, and shift in grade from baseline to the worst post-baseline value will be summarized. Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

Listings of all laboratory data with a flag for cycles with a skipped dose, normal reference ranges, and CTCAE grades (when possible) will be provided.

6.2.8.4. Vital Signs

For vital sign parameters (Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Temperature, and Weight) the observed values and change from baseline will be summarized using descriptive statistics at each visit during the treatment period.

Additionally, the frequency and percentage of patients with any potentially clinically significant findings (defined in Table 14) during the treatment period will be presented. A listing of all vital sign data will be provided.

6.2.8.5. Performance Status

Descriptive statistics will be presented for ECOG score for the observed values and change from baseline. A listing of ECOG score for all patients will be provided.

6.2.8.6. Physical Examination

A listing of screening physical examination findings for all patients will be provided (where available).

6.2.8.7. ECG

Descriptive statistics will be presented for each ECG parameter for the observed values and change from baseline to post baseline. A listing of all ECG data will be provided.

The criteria for potentially clinically significant findings are defined in Table 16. The frequency and percentage of patients with any potentially clinically significant findings during the treatment period will be presented. The supportive data will be provided in patient data listings.

6.2.9. Subgroup Analyses

The PFS, OS, and MAHE will be examined in the following subgroups:

- Age group (ages <65; >65).
- Liver involvement (Yes; No).
- ECOG performance status (0; 1).
- Prior lines of therapy (0; 1-2).
- Race (Caucasian; non-Caucasian).
- Region (US; Ex-US).
- BRCA classification (Positive; Unknown)
- Histological classification (TNBC; Acquired TNBC)

Descriptive statistics by treatment group will be presented for each subgroup of patients. Additional subgroups or endpoints may be identified and explored.

6.2.10. Pharmacokinetic Analysis

The PK analysis for a subset of patients will be documented separately and is not covered in this SAP.

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6.2.12. Planned Analysis

The final myelosuppression analysis will be conducted after all patients have had the opportunity to receive at least 12 weeks of treatment. All study data collected through the time of the final myelosuppression analysis data cut will be included. This includes, but is not limited to the final myelosuppression analysis, interim ORR analysis based on investigator assessment, and interim PFS/OS analysis.

The time of analysis with at least 80% of patients having experienced a progression will be considered to be final PFS analysis. Patients will be followed for survival until at least 70% of the patients have died, and a final OS analysis will be done then. Additional exploratory analyses of OS/PFS may between the final myelosuppression analysis and study completion. Reported results, with the exception of the myelosuppression analyses, will be cumulative in nature, including all data collected during the entire study; the myelosuppression analyses will be complete at the final analysis and no additional data will be expected.

7. CHANGE FROM THE PROTOCOL

The timing of the final analysis, analysis sets, and endpoints were updated based on scientific advice, regulatory guidance, and feedback on other trilaciclib studies. The endpoints and analyses listed below are based on the Statistics Section in the Protocol Amendment 3, dated 31 August 2017. The list displays the endpoints and analyses which are removed from the initial analysis and are therefore not described in the SAP.

Protocol Section 13.3.1 (Efficacy Endpoints):

- Hematologic kinetic endpoints:
    - Change and percent change in hematologic parameter values from predose for a particular cycle to the end of that cycle
    - Change and percent change in hematologic parameter values from predose for a particular cycle to nadir for that cycle
    - Rate of change in hematologic parameter values from predose for a particular cycle to nadir for that cycle
    - Change and percent change in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Rate of change in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Area under the curve in hematologic parameter values from predose for a particular cycle to the end of that cycle
    - Area under the curve in hematologic parameters from predose for a particular cycle to nadir for that cycle
    - Area under the curve in hematologic parameter values from nadir for a particular cycle to the end of that cycle
    - Time to hematologic parameter value nadir by cycle
    - Time to return to predose hematologic parameter values by cycle
    - Proportion of patients with a return to predose hematologic parameter values by cycle
- Hematologic toxicity endpoints:
    - Proportion of patients with a hematologic toxicity recovery by cycle.
    - Time to hematologic toxicity recovery by cycle

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Protocol Section 13.3.2.1 (Analysis of Hematologic Parameter Kinetic Endpoints)

- Additional tabulations for each cycle of treatment in maximum postnadir values.

- The tabulation of the changes and percent changes from predose to nadir, predose to end of cycle, nadir to maximum postnadir, and nadir to end of cycle values for each cycle of treatment.
- Analysis of covariance (ANOVA) models on hematologic parameter kinetic endpoints
- Summarization of time to nadir.
- Descriptive statistics and ANOVA of AUC in hematologic parameters
- Repeated-measures model of AUC
- Summary of proportion of patients return to predose value for each cycle, calculation on incidence rate, adjusting for cumulative exposure
- Analysis of time to return to predose level for each cycle using Kaplan-Meier method.
- Analysis of Time to return to postnadir predose levels

Protocol Section 13.3.2.2 (Analysis of Hematologic Toxicity Endpoints)

- Calculation and analysis of incidence rate of hematologic toxicity, adjusting for cumulative exposure
- Calculation and analysis of toxicity rate relative to cumulative exposure (total number of toxicities divided by cumulative exposure).
- Recurrent events model estimating the incidence of Grade 3 or higher hematologic toxicities and testing for the difference between treatment groups.
- For each hematologic parameter and cycle, the shift summaries of the following:
    - From predose toxicity to maximum on treatment toxicity;
    - from predose toxicity to end of cycle toxicity;
    - from maximum postdose toxicity to end of cycle toxicity.

Protocol Section 13.3.2.4 (Other Efficacy Endpoints)

- The number and percent of infections summarized by maximum severity
- The infection rate: The number of infections occurring during the Treatment divided by cumulative exposure.

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Table A-1 Clinical Laboratory Parameters CTCAE Criteria

Parameter	Grade				
	1	2	3	4	5
Albumin	<LLN – 3 g/dL; <LLN – 30 g/L	<3 – 2 g/dL; <30 – 20 g/L	<2 g/dL; <20 g/L	-	-
ALP	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
ALT	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
AST	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Bilirubin	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN	-
Calcium (Hypercalcemia)	Corrected serum calcium of >ULN – 11.5 mg/dL; >ULN – 2.9 mmol/L	Corrected serum calcium of >11.5 – 12.5 mg/dL; >2.9 – 3.1 mmol/L	Corrected serum calcium of >12.5 – 13.5 mg/dL; >3.1 – 3.4 mmol/L	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L	-
Calcium (Hypocalcemia)	Corrected serum calcium of <LLN – 8.0 mg/dL; <LLN – 2.0 mmol/L	Corrected serum calcium of <8.0 – 7.0 mg/dL; <2.0 – 1.75 mmol/L	Corrected serum calcium of <7.0 – 6.0 mg/dL; <1.75 – 1.5 mmol/L	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L	-
CK	>ULN – 2.5 x ULN	>2.5 x ULN – 5 x ULN	>5 x ULN – 10 x ULN	>10 x ULN	-
Creatinine	>1 – 1.5 x baseline; >ULN – 1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 – 3.0 x ULN	>3.0 x baseline; >3.0 – 6.0 x ULN	>6.0 x ULN	-
GGT	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN	-
Glucose (Hyperglycemia)	Fasting glucose value >ULN – 160 mg/dL; Fasting glucose value >ULN – 8.9 mmol/L	Fasting glucose value >160 – 250 mg/dL; Fasting glucose value >8.9 – 13.9 mmol/L	Fasting glucose value >250 – 500 mg/dL; Fasting glucose value >13.9 – 27.8 mmol/L	Fasting glucose value >500 mg/dL; Fasting glucose value >27.8 mmol/L	-
Glucose (Hypoglycemia)	<LLN – 55 mg/dL; <LLN – 3.0 mmol/L	<55 – 40 mg/dL; <3.0 – 2.2 mmol/L	<40 – 30 mg/dL; <2.2 – 1.7 mmol/L mmol/L	<30 mg/dL; <1.7 mmol/L	-
Hemoglobin	<LLN – 10.0 g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L	<10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-	-
Potassium (Hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L	>7.0 mmol/L	-

Table A-1 Clinical Laboratory Parameters CTCAE Criteria

Parameter	Grade				
	1	2	3	4	5
Potassium (Hypokalemia)	<LLN – 3.0 mmol/L	-	<3.0 – 2.5 mmol/L	<2.5 mmol/L	-
Lymphocyte	<LLN – 800/mm3; <LLN – 0.8 x 10e9 /L	<800 – 500/mm3; <0.8 – 0.5 x 10e9 /L	<500 – 200/mm3; <0.5 – 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
ANC	<LLN – 1500/mm3; <LLN – 1.5 x 10e9 /L	<1500 – 1000/mm3; <1.5 – 1.0 x 10e9 /L	<1000 – 500/mm3; <1.0 – 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Phosphates	<LLN – 2.5 mg/dL; <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL; <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL; 0.6 – 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L	-
Platelet Count	<LLN – 75,000/mm3; <LLN – 75.0 x 10e9 /L	<75,000 – 50,000/mm3; <75.0 – 50.0 x 10e9 /L	<50,000 – 25,000/mm3; <50.0 – 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Sodium (Hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L	>160 mmol/L	-
Sodium (Hyponatremia)	<LLN – 130 mmol/L	-	<130 – 120 mmol/L	<120 mmol/L	-
Urate	>ULN – 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN – 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L	-
White blood cell	<LLN – 3000/mm3; <LLN – 3.0 x 10e9 /L	<3000 – 2000/mm3; <3.0 – 2.0 x 10e9 /L	<2000 – 1000/mm3; <2.0 – 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-

LLN=lower limit of normal range; ULN=upper limit of normal range.